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A COMPARISON OF PARADIONE AND TRIDIONE IN THE TREATMENT OF EPILEPSY

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THE value of trimethyloxazolidine dione (Tridione) in the treatment of petit mal epilepsy has been abundantly demonstrated.[1, 2, 3] However, reports of side effects, notably the induction of aplastic anemia in a handful of cases,[4] have sharpened the search for an analogue that might be equally helpful clinically but have less toxic action. The manufacturers of Tridione have developed the analogue dimethylethyl oxazolidine dione which they have named Paradione. The drug has been given the required tests for toxicity in the pharmacology department of Abbott and Company, but it is not yet on the market. Dr. R. K. Richards kindly supplied us with material.

The structural formula of Paradione differs from that of Tridione in the substitution of an ethyl for a methyl group on carbon 5. It is an oily liquid, slightly soluble in water but easily soluble in alcohol. It is supplied as an elixir (32 per cent alcohol) in which a fluid ounce contains 3 Gm., or a teaspoonful (4 c.c.) contains 375 mg. It is also put up in gelatin capsules, each containing 300 mg. Patients treated by us, if under 6 years of age, were given 8 c.c. or 750 mg. daily, and if above that age, from 12 to 24 c.c. daily. The dosage of Tridione was similar.

We have used Paradione during the past two years in a total of eighty-five patients. Its action in forty-seven patients has been published.[5] The present report deals with seventy-three patients subject to petit mal who took Tridione and Paradione successively, thirty-one patients subject to grand mal and nine subject to psychomotor seizures. Some experienced more than one type of seizure. The great majority of the patients were children. We were concerned first with the therapeutic effect of Paradione in various types of seizures, and second with the presence or absence of side effects.

PETIT MAL TRIAD

Most interest attaches to the patients who took both Tridione and Paradione. The periods of medication were comparable for the two drugs. Tridione was

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used first. Paradione was substituted because Tridione failed to control seizures (70 per cent), or it caused unpleasant side effects (25 per cent) or the substitution was experimental (5 per cent).

There was no uniformity in the anti-petit mal action of these two drugs; patient A would prefer Tridione and patient B Paradione. In order to avoid a complicated presentation of data, we compare the therapeutic effects of the two drugs in the whole group of patients rather than in individuals. The reader should understand that this is a selected group of patients, selected in large part because of failure to respond satisfactorily to Tridione. Therefore, results do not represent the value of these drugs in the treatment of petit mal. Thus, in an unselected group of patients, 63 per cent were substantially improved by Tridione[1] against only 23 per cent in the present group.

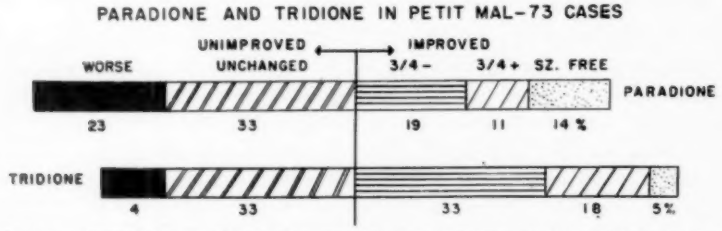

Fig. 1.—Comparison of therapeutic results from Tridione and Paradione in the same seventy-three patients subject to petit mal. The portion of the columns to the right of the perpendicular represents various degrees of improvement, namely 100 per cent, 75 per cent or more, and less than 75 per cent. To the left are patients not improved, or (solid portion) those made worse.

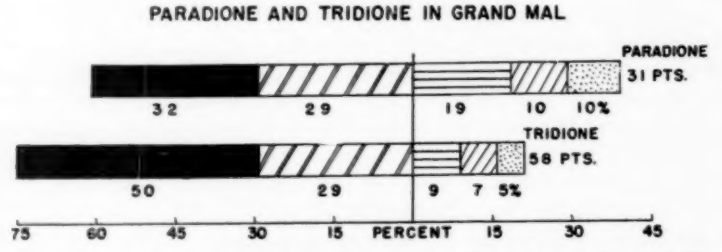

Fig. 2.—Comparison of therapeutic effect on grand mal in thirty-one patients taking Paradione, and another fifty-eight patients taking Tridione. The symbols are the same as in Fig. 1.

Results in these seventy-three patients are displayed graphically in Fig. 1. The number of patients who lost three-fourths or more of their seizures was approximately the same whether Tridione or Paradione was used. (23 and 25 per cent respectively). When taking Paradione, more patients were seizure free, but also more were worse than when taking Tridione. For the whole group, this tabulation suggests that the action of the two drugs does not differ significantly. However, we have the general impression that Tridione is usually the more effective of the two. Only 5 per cent of the total group responded well to both drugs; the rest were greatly helped by only one of the two homologues.

The physician deals not with a group average, but with a succession of individuals. For each of these the effect of medication is unpredictable. A number of the patients treated had fewer seizures with Paradione than with Tridione. This consideration should make Paradione a useful substitute in therapy.

GRAND MAL

Thirty-one patients having grand mal, usually in addition to petit mal, were treated with Paradione, often combined with an anticonvulsant. Results in this group, compared with results with Tridione in a group of fifty-eight patients previously reported[1] is shown in Fig. 2. Because these two groups of patients are not identical, comparison is not exact. However, the data suggest that Paradione is not as much of a convulsant for patients as Tridione and, therefore, would be preferable for use in persons whose petit mal condition is complicated by grand mal.

PSYCHOMOTOR

Although DeJong[6] recommended Tridione (in addition to an anticonvulsant) for patients subject to psychomotor seizures, other investigators have not confirmed his optimistic reports. Our own results have been equivocal. In thirty-five cases previously reported,[1] 45 per cent were somewhat better. With Paradione, three out of nine psychomotor patients in the present series were improved.

SIDE EFFECTS

Many a promising anticonvulsant has had to be abandoned because of unpleasant or dangerous side effects. Those side-effects attending the use of Tridione have been peculiar or disconcerting. The principal ones are neutropenia, rash, photophobia, and sedation, the last named expressed as drowsiness, lethargy, or fatigue.

Comparison of the incidence of these symptoms in the 73 patients taking both of the diones is shown in Table I.

TABLE I. SIDE EFFECTS IN SEVENTY-THREE PATIENTS

	PARADIONE		TRIDIONE	
	NO.	%	NO.	%
Neutropenia				
1,600 to 2,200 per cubic millimeter	5	8	6	8
Below 1,600	4	6	9	13
Rash	11	15	15	21
Photophobia	9	13	24	33
Lethargy	8	11	3	4

We emphasize that the incidence of toxic reactions is high in this group of patients because of its selection. One-fourth were changed from Tridione to Paradione in the effort to avoid the side effects of Tridione. Of these various side effects, depression of the bone marrow, although relatively infrequent, is most serious. Thus, among 123 unselected patients treated for petit mal with Tridione only 6 per cent developed neutropenia of 1,600 cubic millimeters or

less.[4] Experience of others has varied greatly; for example, neutropenia was not observed in thirty patients treated with Tridione in the New Haven Clinic.[7] Severe neutropenia (a neutrophile count of 1,600 per cubic millimeter or less) occurred in 13 per cent of the present group of patients taking Tridione compared with 6 per cent taking Paradione.

Among these seventy-three patients, ten had an unfavorable blood reaction to Tridione but not to paradione; six reacted to both drugs, the reaction to both being severe in one case, more severe to Tridione in four, and more severe to Paradione in one case; three reacted to Paradione but not to Tridione. Thus, on all counts the Paradione would seem to have somewhat less toxic action on the bone marrow. This differential has permitted some patients to remain free of petit mal who otherwise would have had to cease medication with consequent return of seizures. The rule of stopping medication when this degree of neutropenia (1,600 per cubic millimeter) is reached, is of course, arbitrary. Possibly no harm would result from a neutrophile count that is persistently below 1,600 per cubic millimeter. We did not attempt to find out.

The case of L. B., first recorded in December, 1945,[1] illustrates the difficulty often encountered in maintaining medication and shows the comparative action of Tridione and of Paradione over periods of nineteen and twenty-two months, respectively. This child was born in February, 1942. A few days later ptosis of the left eyelid was noted. At 15 months of age she began to have a few clonic jerks of her extremities whenever she tripped or was startled by a noise. At 36 months she began to fall and jerk without tripping and to blink her eyes briefly (akinetic and pyknoleptic manifestations of petit mal). The akinetic attacks rapidly became more frequent. She would fall from fifty to 200 times a day. Phenobarbital gave a respite of only six days. The child was mentally retarded and her behavior was atrocious.

In March, 1945, Tridione, 0.9 Gm. a day, was prescribed. After twelve hours all seizures ceased. During the three and three-fourths years that have intervened the child has been almost free of seizures except when medication was interrupted. However, the dosage has had to be adjusted frequently. An incomplete fall or an episode of blinking could be observed several times a month and persisted even with a dose of 1.5 Gm. of Tridione daily. However, after the first six months the child made steady progress in mental development and in deportment. The necessity of periodic blood examinations was not realized until sixteen months after starting Tridione. Neutrophiles then numbered 3,400 per cubic millimeter, but two months later the count was only 1,700 and Tridione was stopped. Four days later neutrophiles had increased to 2,900 per cubic millimeter. The child began again to fall and on Oct. 4, 1948, Paradione was substituted.

The father of L. B. is a physician and forty-four blood examinations were made during the twenty-five months of Paradione medication. On four occasions the neutrophile count fell below 1,600. On the first three occasions, Paradione was stopped and akinetic attacks promptly recurred. Phenobarbital relieved for six days and bromides not at all. Four months later the neutrophiles numbered only 1,100 per cubic millimeter, but in four medicineless days

rose to their usual level of 2,500 per cubic millimeter. For the next twelve months the dose of Paradione was from 0.6 to 0.9 Gm. daily, together with 10 to 15 mg. of folic acid. Neutrophiles numbered from 2,000 to 3,100 per cubic millimeter, eosinophiles from 3 to 17 per cent and an incomplete fall or blinking was observed only at intervals of weeks. Although much improved, the electroencephalogram still contains spike and wave discharges. On June 15, 1948, a neutrophile count of 960 was obtained. Paradione was stopped for two days and then resumed at 0.3 Gm. daily. Four examinations made during the following six weeks revealed neutrophile counts ranging from 1,140 to 2,200 per cubic millimeter. On July 31, 1948, phenacetylurea (Phenurone) was added. After a rash, an infection, and another dip to 1000 neutrophiles, affairs stabilized and the child has been symptom-free with normal blood for three months, taking only 0.3 Gm. Paradione and 0.5 Gm. Phenurone daily.

As regards the complication of cutaneous rash, experience with the two drugs was much the same; i.e., 15 per cent experienced a generalized rash with Paradione against 21 per cent with Tridione. Of eleven patients who displayed an eruption while taking Paradione, in five the rash was morbiliform, in three urticarial, and in one each eczematoid, hemorrhagic, and acneiform. Of the fifteen patients taking Tridione, twelve had a morbiliform, two an acneiform, and one an eczematoid type of reaction. Paradione might have been favored by the circumstance that Tridione was given first. This may have had the effect of desensitizing patients. Some persons who have a rash when medication is first instituted will not erupt when, after an interval, the drug is reinstated.

Hemeralopia (photophobia) is a curious side effect of Tridione the mechanism of which is as yet unexplained. It apparently has no lasting ill effect but may cause much discomfort to those severely affected. Paradione proved distinctly superior to Tridione in this respect. Only 13 per cent of patients of this selected group complained of photophobia when taking Paradione, against 33 per cent when taking Tridione. Patients would again suffer from photophobia when Tridione was substituted for Paradione, thus proving that accommodation to the dione was not responsible for the greater eye comfort of Paradione.

An infrequent side effect of the oxazolidine diones is lethargy. In contrast with the other symptoms, complaints were more frequent against Paradione (11 per cent) than against Tridione (4 per cent). The larger percentage of patients who complained of lethargy on Paradione is probably a reflection of its greater sedative action as demonstrated in laboratory animals.[8] No patients stopped medication because of this symptom, although it limited the dosages prescribed for a few children.

Nephrosis is a rare complication that has been reported but once in a patient taking Tridione.[9] One of our patients, a child of six, had petit mal seizures that were incompletely controlled with Tridione. Paradione was substituted and after a stormy period of prolonged petit mal status, seizures ceased. Some months later nephrosis developed and Paradione was discontinued without return of seizures.

DISCUSSION

Comparison of these two drugs has shown that their over-all effects are similar, but some patients who fail to respond to one of them may be greatly improved by the other. The results for any given patient cannot be predicted beforehand, either from the duration or the type of seizures, or from the pattern of the spike and wave discharge in the electroencephalogram. For those who have grand mal associated with petit mal, Paradione seems to have the advantage of being less of a convulsant. A patient who experiences unpleasant side effects with one may have no difficulty with the other. If we could have but one of these drugs, the less toxic effects of Paradione probably would overbalance its somewhat smaller effectiveness and its greater cost. However, the individuality of response to medication and the urgent need for help are so great that physicians should, if possible, have access to both of the oxazolidine diones.

CONCLUSIONS

In epileptic patients, Paradione seems to have less convulsive action than Tridione. The effect of the two drugs on petit mal was compared directly in seventy-three patients. In general, Paradione was no more effective in stopping petit mal than Tridione, but it caused much less photophobia and somewhat less neutropenia. The hypnotic effect was greater. Paradione proves either more effective or less toxic than Tridione in enough individuals that this drug should be available to physicians in their treatment of patients with petit mal.

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STREPTOMYCIN THERAPY FOR PERTUSSIS

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THE use of streptomycin in treatment of twenty-seven patients with severe whooping cough significantly reduced the death rate of infants and small children. The death rate in a control group of twenty-eight patients was more than five times that of the treated group.

All discussions of pertussis stress the seriousness of this disease in the first six months of life. Fatality rates for this age group are variously quoted as ranging from 30 to 50 per cent.[1, 2] Over the age of 5 years the disease is rarely fatal. The mortality rate for the United States is 2.3 per cent and the case fatality rate in Arkansas for 1947 was 3.3 per cent.[3] If the case fatality in Arkansas by age groups is further analyzed, it is found that 40 per cent of the deaths occur in children under 3 months of age, 28.5 per cent in children under 4 to 6 months or 68.5 per cent in those under 6 months of age. Fortunately the invaluable contribution of McGuinness and associates,[4, 5, 6] in the development of hyperimmune human antipertussis serum has already given the physician a potent weapon with which to combat the disease. The use of antibiotic agents provides an additional means of therapy.

The studies in many investigators have indicated that streptomycin is effective against the *Hemophilus pertussis* in vitro. On the basis of these results this study of the clinical effect of the drug was undertaken shortly after the antibiotic was released from the control of the Committee on Chemotherapeutics of the National Research Council and has continued up to the present time.

No selection of cases was practiced since it was the policy to admit to the isolation wards of the University Hospital only severe cases usually with complications or infants under one year of age.

The criteria for establishing the diagnosis of whooping cough were as follows:

1. A positive culture for *H. pertussis* plus evidence of respiratory infection.
2. A respiratory infection characterized by paroxysmal coughing and leucocytosis with a definite increase in lymphocyte count plus any or all of the following supplementary factors:
   A. History of pertussis in siblings or history of close contact with active cases.
   B. Vomiting following paroxysms.
   C. Characteristic whoop of recent onset.

Patients more than 8 months of age were admitted only if the disease was severe. Severity was judged by the presence of conjunctival ecchymoses, en-

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cephalopathy, dehydration resulting from severe vomiting or evidence of pneumonia. A diagnosis of pneumonia as a complication was based on physical findings, fever, x-ray of the chest, or all three combined. Pneumonia is the most common complication of whooping cough. It usually is found in most patients who die of pertussis. The following pathologic changes occur: scattered areas of consolidation, atelectasis, peribronchial infiltration with involvement of adjacent alveoli, and interstitial thickening of the alveolar walls.[7] In this study fourteen cases in the treated group and seventeen in the control group were complicated by pneumonia. Eight patients of the treated group and ten of the control group were under 8 months of age.

The patients who met the above requirements for diagnosis and had been admitted during approximately the three years prior to the advent of the streptomycin therapy were considered to be suitable for classification as control cases. By sheer chance, the number of these patients has been found to be practically equal to those who have received treatment to date.

Since we were aware of no published data to guide in determination of the dosage of streptomycin, it was decided to adopt the dosage recommended by the Committee on Chemotherapeutics of the National Research Council for treatment of *Hemophilus influenzae* meningitis. Accordingly, 25 mg. per pound of body weight was considered to be the total daily dose. The total dose was divided into eight equal parts and administered by the intramuscular route every three hours. The range of the number of days during which patients were treated with streptomycin was one to sixteen and the arithmetic mean of this range was seven days per patient. In most of the patients, treatment was continued for three to four days after the temperature was normal. Nineteen of the patients treated with streptomycin also were treated with sulfadiazine or penicillin or both for complicating secondary infection but without any noticeable improvement of the whooping cough. Sedation and oxygen therapy for cyanosis and control of paroxysms were used in both groups. In 1940 Kohn[8] reported thirty-three patients with pertussis pneumonia treated with sulfadiazine and noted no significant improvement in results other than had been obtained by supportive therapy alone. In our series, twenty of the control group received sulfadiazine or penicillin before the advent of streptomycin and results show a high death rate.

The number and severity of paroxysms were charted for each twenty-four hours, as was the frequency of vomiting and recurrent cyanosis.

Improvement was considered to be definite when the severity and number of paroxysms decreased, the infant was able to nurse, vomiting diminished, and cyanosis became less frequent. In the majority of instances, some improvement was noted within twenty-four to forty-eight hours as seen in Table I, and definite

TABLE I. DAYS REQUIRED FOR SIGNIFICANT IMPROVEMENT ACCORDING TO AGE DISTRIBUTION

NO. CASES	AGE DISTRIBUTION	RANGE	ARITHMETIC MEAN
19	0 to 8 months	0.5 to 10	3
4	8 mo. to 3 years	1 to 5	2.5
4	3 years and over	1 to 5	4

improvement occurred in three to four days. In three cases definite improvement was not noted until seven to ten days had elapsed. Positive cultures for *H. pertussis* were obtained in five of the twenty-seven cases. These five patients had been ill only one week prior to admission.

An analysis of the effect of streptomycin therapy on the number of days required for hospitalization revealed no significant difference between the treated and the control group as is shown in Table II. However, it is likely that the duration of treatment could be reduced by a day or two.

The difference in the case fatality rate is most striking. This is presented in Table III. The case fatality rate in the control group is 39.3 per cent and is 7.4 per cent in the treated group. The actual difference in fatality between the control and treated is 31.9 per cent. The standard error of difference between the two values for case fatality, namely control and treated groups, is plus or minus 10.5 per cent. In other words, the actual difference in case fatality in the two groups is slightly more than three times the standard error.

TABLE II. TOTAL HOSPITAL DAYS AND DAYS OF ILLNESS PRIOR TO ADMISSION TO THE HOSPITAL ACCORDING TO AGE DISTRIBUTION

AGE DISTRIBUTION	NO CASES	TOTAL HOSPITAL DAYS		DAYS OF ILLNESS PRIOR TO ADMISSION	
		RANGE	ARITHMETIC MEAN	RANGE	ARITHMETIC MEAN
0 to 8 months					
Treated	19	5-21	8	4-52	10
Control	13	1-28	7	6-42	14
8 months to 3 years					
Treated	4	2-17	6.5	5-35	21
Control	9	1-29	9	12-48	28
3 years and over					
Treated	4	9-16	12.5	4-25	14
Control	6	3-32	14	10-49	21.5

TABLE III. COMPARISON OF CASE FATALITY RATES OF VARIOUS AGE GROUPS OF TREATED AND CONTROL CASES

AGE DISTRIBUTION	NO CASES	TYPE OF CASE		RESULTS			
		SEVERE	COMPLICATED BY PNEUMONIA	IMPROVED	UNCHANGED	DIED NO.	DIED %
0 to 8 months							
Treated	19	11	8	16	1	2	10.5
Control	13	3	10	6	0	7	53.8
8 months to 3 years							
Treated	4	0	4	4	0	0	0
Control	9	2	7	7	0	2	28.5
3 years and over							
Treated	4	2	2	4	0	0	0
Control	6	6	0	4	0	2	33.3
All ages							
Treated	27	13	14	24	1	2	7.4
Control	28	11	17	17	0	11	39.3

Standard error of difference ± 10.5.
Actual per cent of difference in case fatality 31.9.

DISCUSSION

Although the number of cases presented is not great, it is felt that the controls represent a group similar to the treated group and that essentially the

two groups come from the same "universe." Because of this fact plus the significant results obtained, it is felt that it is justified to conclude that streptomycin in the dosage administered was of definite value in the reduction of the mortality in whooping cough, especially in the age group of 0 to 8 months and in those cases complicated by pneumonia, and that its effectiveness in clinical therapy of *H. pertussis* infection parallels its effectiveness against the organism in vitro and in experimental infection as suggested by Alexander.[9] In 1946 Alexander made the statement that the results of in vitro sensitivity tests provided an index of therapeutic effectiveness of streptomycin in *H. influenzae* meningitis and that the same in vitro tests showed that the range of sensitivity of *H. pertussis* was not significantly increased over that of *H. influenzae*. She stated at that time that there was reason to believe that streptomycin would prove an effective agent against *H. pertussis* infection but that clinical trial was inadequate for evaluation. In 1948 Coffey and Levy[10] reported six patients with pertussis pneumonia treated with streptomycin. Two of these patients died and four showed marked clinical improvement within forty-eight hours of the time that streptomycin therapy was started. The larger series presented in our paper accentuates the favorable results that may be expected.

Dowling[11] has reported that fourteen seriously ill patients under 7 months of age showed clinical improvement after receiving 25 mg. of streptomycin intramuscularly at three-hour intervals for five days. No statement was made regarding the occurrence of pneumonia as a complication. No difference in period of hospitalization was noted between the fourteen treated patients and twenty control patients of the same age group. No deaths were noted in either group.

Because of the need for numerous injections, streptomycin is necessarily a treatment for the hospitalized patient. Our results suggest that it should be used on the critically ill patients in addition to hyperimmune serum. Hyperimmune serum probably will continue to be of inestimable value in the treatment of the very ill patient who of necessity must remain at home.

Two newer antibiotic agents show promise of being effective in the treatment of pertussis. Swift[12] treated ten children aged one month to 2.5 years with aerosporin and noted beneficial results when treatment was started early in the course of the disease. Aerosporin is a product derived from the culture of *Bacillus aerosporus Greer* isolated by Ainsworth, Brown, and Brownlee.[13] This product was similar to, but not identical with, polymyxin obtained from filtrates of cultures of *Bacillus polymyxa* by Benedict and Langlykke[14] and by Stansly, Shepherd, and White.[15]

Polymyxin has been found to have a therapeutic effect against pertussis by Schoenbach, Bryer, Bliss, and Long.[16] According to Long, polymyxin has been found to comprise a mixture of antibiotic substances and refinements in production are still necessary. Long and his associates have found that polymyxin causes transitory renal damage in its present form.[17] Polymyxin is definitely more toxic than streptomycin at the present time.

So far as could be ascertained, no vestibular damage occurred nor were any other unfavorable reactions noted attributable to the use of streptomycin in our series of cases.

CONCLUSIONS

1. The use of streptomycin in a dosage of 25 mg. per pound of body weight caused a definite and rapid improvement of twenty-four patients with severe pertussis.

2. Comparison of the case fatality rate of the group of twenty-eight controls and twenty-seven treated patients revealed a statistically significant reduction in the treated group. The actual difference in the case fatality in the two groups is slightly more than three times the standard error.

3. No significant improvement in the length of hospitalization was noted in the treated group as compared to the control group.

4. Streptomycin in conjunction with hyperimmune serum should be used on all critically ill hospitalized pertussis patients.

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ACCIDENTAL VACCINIA: REPORT OF TWO CASES IN INFANTS, WITH ECZEMA VACCINATUM IN ONE CASE

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ACCIDENTAL vaccinia is the condition which results from fortuitous contamination of a person with the virus of vaccinia by direct contact with smallpox vaccine or with an active lesion after smallpox inoculation. In view of the number of vaccinations that are performed, accidental vaccination occurs infrequently. Berggreen[1] in 1936 reported that between the years 1920 and 1935 only ten cases of accidental vaccination were observed at the Berlin Haut Polyklinik. A review of the literature revealed that the most frequent location of accidental inoculation is the region of the eyes. Since Jenner introduced vaccination for smallpox in 1796, approximately 100 cases of ocular complications from accidental contamination have been reported. The eyelids rather than the eyeballs are the usual sites of involvement. Less frequently the conjunctiva and cornea are involved. Disciform keratitis, resulting from accidental vaccinia has been reported recently by Brav.[2] Another less frequent location of accidental vaccination is the nasal region. In 1942, Ayo and Braley[3] collected from the literature sixteen cases of accidental vaccination of the nose. The face, tongue, fingers, and the external genital organs also may be sites of accidental inoculation.

Accidental vaccination usually occurs in nonimmunized persons who have come in contact with an active primary vaccinia. The spread is usually from a newly vaccinated sibling to a nonimmunized sibling or parent, or it may be from a newly vaccinated adult to a nonimmunized member of the family. However, there have been several cases of accidental vaccinia among laboratory workers who help to prepare vaccine. Horgan and Haseeb[4] reported a series of repeated accidental vaccinations among workers who possessed strong or complete vaccinal immunity.

As is well known, there may be three types of reactions to the usual inoculation for smallpox: (1) primary vaccinia or normal take, (2) an accelerated reaction, or (3) an immune reaction.[5] If the technique is faulty or the vaccine impotent, there may be no reaction. The primary vaccinia or normal take is the usual response of the nonimmunized person. This consists of the progressive development of a single papular-vesicular-pustular lesion at the site of the inoculation during a period of about two weeks. The papule develops by the third or fourth day after vaccination. The papule becomes a vesicle on about the fifth day. By the seventh day a red areola is present around the vesicle. During this time the vesicle becomes pustular. It is the discharge from such a vesicle that usually serves as the source for accidental

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vaccination. By the seventh day after vaccination the vesicle begins to dry and the formation of a crust occurs. By the eighteenth day after vaccination the crust usually becomes detached.

An accelerated reaction is seen in persons who have been immunized previously but who do not have total immunity. The reaction is similar to that of primary vaccinia but the process is completed in a much shorter time, within eight or ten days. The crust is small and the scar is minimal.

An immune reaction occurs in those individuals who have been totally immunized against smallpox, either by having been previously vaccinated successfully or by having had smallpox. This reaction consists of the development of an area of redness at the site of inoculation within twenty-four to forty-eight hours after vaccination. A small papule may result but it does not progress to the vesicular stage.

The vesicle of the lesion due to accidental vaccination in the nonimmunized person usually appears from two to three weeks after the time of inoculation of the person from whom the accidental contamination has occurred. Therefore, it represents a primary reaction or a normal take. When vesicles of accidental vaccination develop within a shorter time after inoculation for smallpox, the reaction probably is of the accelerated type. Immune reactions probably occur in accidental vaccinations but the consequences are so slight that they may pass unnoticed.

Complications of primary vaccinia are many but occur infrequently. Probably the most common are the benign exanthemas and multiform eruptions that occur after vaccination. Bloch[6] reported that in 500,000 individuals vaccinated in Glasgow at the time of the 1942 smallpox scare, 123 had postvaccinal eruptions. None of these eruptions were classified as that of generalized vaccinia, that is, a disseminated vaccinal eruption. The majority of the eruptions were erythematous or urticarial in nature. There were a few purpuric reactions. Some were reported as pustular and some as eczematoid. The interval between the time of vaccination and the time of eruption in most cases was from seven to eleven days. Paschen[7] in 1932 gave an excellent classification of postvaccinal eruptions.

Autoinoculation is another complication which may occur. This probably is the most common cause of ocular complications after vaccination. One of the most serious complications of vaccination occurs when children who have eczema are vaccinated. This condition is known as "eczema vaccinatum." Lesions of vaccinia usually occur in the same locations as the preexisting cutaneous lesions.

Most of the other complications of vaccinations are rare. Postvaccinal encephalitis was seen in the Glasgow smallpox scare in a ratio of 1:70,000 vaccinations.[8] Thompson[9] in 1931 reported an incidence of 1:12,000 to 1:330,000. Encephalitis usually occurs between the sixth to fourteenth day after vaccination. Myelitis,[10-12] neuronitis,[13] polyneuritis,[14] retinitis,[14-16] and orchitis[17] have followed vaccination. Infections of bones and joints with vaccinia also have been cited.[18] Tetanus[19, 20] and syphilis have been known

to develop from secondary infection of the vaccination. Both Schönlein-Henoch purpura[21] and thrombocytopenic purpura[22] have been reported after primary vaccinia and generalized vaccinia, respectively. Uncomplicated generalized vaccinia has been reported by Jubb[23] to occur once in 20,000 vaccinations. He reported the mortality rate from it as between 10 and 30 per cent. The mortality rate in eczema vaccinatum reported by McKhann and Ross[24] was 33 per cent.

Any of the various complications mentioned may occur with accidental vaccinations also. The most common are the ocular complications involving the eyelids, conjunctiva and cornea. The most serious are the cases of eczema vaccinatum. Riley and Callaway[25] reported two cases of eczema vaccinatum and reviewed the literature in 1947. In one of the two cases which we are reporting in this paper eczema vaccinatum occurred.

Fig. 1.—Case 1. Accidental vaccination of right cheek of a male child 18 months old.

CASE REPORTS

CASE 1.—A white male child aged 18 months was admitted to the Mayo Clinic and immediately hospitalized because of a large, single, pustular lesion on the right cheek. Nine days before his admission to the hospital both of his older sisters, aged 7 and 9 years, had been vaccinated for smallpox. Neither sibling had been vaccinated previously. The older sibling exhibited an immune reaction and the younger one demonstrated an accelerated reaction. Five days after the siblings were vaccinated, erythema developed on the patient's right cheek. This became papular and finally a pustule developed. An attempt was made to rupture this pustule with a needle. After this, the

lesion began to discharge seropurulent material. The day before admission the lesion was the size of a dime and had begun to crust. Seropurulent discharge exuded from beneath the crust. The region of erythema became larger, measuring 3 or 4 cm. in diameter, and involved the entire right cheek and eyelid. The right eye was swollen shut.

The child's rectal temperature at the time of admission to the hospital was 101.2° F. Physical examination revealed the lesion described with a few small secondary papules just below it. At this time the major lesion resembled that usually seen eight or nine days after vaccination for smallpox. Material from the lesion was cultured but results were reported to be negative. A positive Paul test[26] was not obtained. Values for hemoglobin and erythrocyte, leucocyte, and differential blood counts were normal. The edematous lesion was treated with moist compresses. Because it appeared to be secondarily infected and fever was present, 80,000 units of penicillin were administered intramuscularly each day as a precautionary measure. By the fourth day in the hospital the secondary infection had disappeared and the papule had a well-defined crust. The edema and erythema had disappeared and the lesion resembled that following vaccination for smallpox.

The child was dismissed from the hospital on the tenth day. Three months later the child was vaccinated against smallpox; there was no reaction. Eleven days later the child was revaccinated; forty-eight hours afterward there were definite signs of an immune reaction with redness, some induration, and three minute vesicles.

CASE 2.—A white male child aged 6½ months was brought to the clinic and was hospitalized immediately because of a severe skin disorder. The baby had first exhibited signs of eczema at 7 weeks of age. The eruption had started on the cheeks and had spread to the ears, forehead, and scalp. When he was 10 weeks of age the extremities had become involved. Numerous attempts had been made to control the eczema by dietary means without success.

The family history was not known. The child had been adopted at the age of 17 days. He had not been immunized against any contagious disease. However, his foster mother had been vaccinated fifteen days previously against smallpox and had had an accelerated reaction. Thirteen days after the mother's vaccination, pustules developed in the dry eczematous region above the baby's right eye and on his left cheek. The next morning the face began to swell. The entire face rapidly became similarly involved. He was admitted to the hospital about twenty-four hours later.

At time of admission the rectal temperature was 103.2° F. The entire face was covered with moist, bleeding, umbilicated pustules. The eyes were swollen shut. The anterior surface of the chest and abdomen were less markedly but similarly involved with umbilicated lesions. A diagnosis of eczema vaccinatum was made.

Cultures of material taken from the lesions on the face revealed hemolytic streptococci and Pseudomonas. The vaccinal virus was proved to be present by the Paul test. Penicillin in daily doses of 160,000 units was administered intramuscularly to combat the secondary infection. Elixir of phenobarbital and acetylsalicylic acid were employed as sedatives. The mother's blood was group A, which was unsuitable for the baby. Plasma, therefore, was extracted from the mother's blood and 20 c.c. of it were given intramuscularly each day to the child for the first three days.

During the first three days in the hospital the child's temperature taken by rectum varied from 102° to 105° F. On the fourth day it fell to 99° F. After

this, there was a secondary rise to 103° F. The temperature did not return to normal until the eighth day, after which time it remained normal until dismissal on the fifteenth day.

On admission the value for hemoglobin was 13.2 Gm. per 100 c.c. of blood. The erythrocyte count was 4,730,000 per cubic millimeter of blood. The leucocyte count was 14,300 per cubic millimeter; 17 per cent of these were lymphocytes, 14 per cent monocytes, 2 per cent eosinophiles, and 9 per cent filamented and 58 per cent nonfilamented polymorphonuclear neutrophiles.

Fig. 2.—Case 2. Eczema vaccinatum in a male child 6 months old.

On the second day in the hospital the lesions on the face and forehead were confluent and pustular. There were scattered discrete lesions on the chest, abdomen, and extremities. Mild antiseptic packs were applied. By the third day after admission, most of the pustules on the face had ruptured. The face exhibited a reddish, moist appearance. By the fourth day the lesions on the trunk were drying and there was further improvement. At this time the leucocyte count had dropped to 9,000 cells per cubic millimeter of blood. Urinalysis revealed nothing abnormal. One week after admission mild topical ointment was applied to the healed lesions. The child was dismissed two weeks after admission. There was no scarring of the face on dismissal.

COMMENT

In Case 1, the accidental vaccinal reaction which occurred on the child's right cheek appears to have been of the accelerated type because it developed to a papular stage within five days after the siblings had been vaccinated. The lesion no doubt had been secondarily infected at the time it had been ruptured

with a needle. This probably shortened the period between the vesicular and pustular stages. The secondary infection and the precarious location near the right eye were the gravest factors in this case. In spite of the considerable inflammatory reaction with edema of the eyelids, the bulb of the eye was not involved. Although a positive Paul test was not obtained in this case, an active immunity to smallpox apparently developed from this accidental vaccination, as was proved by the immune reaction which followed vaccination for smallpox three and one-half months later.

In Case 2, an eczematous infant was accidentally inoculated with vaccinia as a result of contact with the vaccination of his foster mother. The time interval of thirteen days between the mother's vaccination and the appearance of the baby's lesion showed that the child possessed no immunity and would probably have had a single lesion of primary vaccinia if he had not had the eczematous condition. The hypersusceptibility of persons who have cutaneous disease to the vaccinia virus is striking. This may be related to an allergic reaction, which has been suggested by various authors,[27-29] particularly in the development of generalized vaccinia. The rapid toxic reaction which the second patient showed could be due also to the effect of the secondary hemolytic streptococcic infection. This infection was brought under control with penicillin and antiseptic compresses. Passive immunity to vaccinia was attempted by giving the mother's plasma to the child.

Positive proof that vaccinia was the source of this condition was shown by a positive Paul test. This test consists of inoculating the scarified eye of a rabbit with the seropurulent material from the lesion. Within thirty-six hours the rabbit's cornea will show definite changes if the vaccinia virus is present. Fixation of the enucleated eye for one minute in a solution of 2 parts of 6 per cent mercury bichloride and 1 part dehydrated alcohol causes the isolated, intensely white, opaque elevations to be seen on the cornea. Histologic section through this part of the cornea may show Guarnieri bodies which are thought to be specific for the vaccinia virus. A positive result of the Paul test is considered pathognomonic for smallpox and is useful in differentiating this condition from other virus infections, particularly varicella.

The spread of vaccinia from the initial site of inoculation, accidental or otherwise, is considered to be by way of the blood stream.[30] It has been demonstrated that within four or five days after vaccination, the vaccinia virus may be present in the nasopharynx and that dissemination through the body is hematogenous.[31]

As was seen in Case 1, active immunity developed from accidental vaccination. No attempt was made to revaccinate the eczematous child in order to prove his immunity. Busch[32] reported a case in which a boy had two attacks of eczema vaccinatum within a period of four years. The second attack was fatal. The presence of severe secondary infection rather than the direct effect of the vaccinia virus may have caused the death. If total immunity had been developed by the primary attack, the second attack of eczema vaccinatum would not have developed.

In the literature there has been considerable discussion concerning the relationship of eczema vaccinatum and Kaposi's varicelliform eruption. Tedder[33] in 1936 and Ronchese[34] in 1943 stated that eczema vaccinatum and Kaposi's varicelliform eruption seemed to be identical conditions. Although both occur among persons who have eczema, recent evidence indicates that Kaposi's varicelliform eruption is due to the virus of herpes simplex. Lane and Herold[35] in 1944 stated that the two conditions can be differentiated. Hershey and Smith[36] in 1945 concluded that the vaccinia virus and the herpes virus are capable of producing similar eruptions in the skin of eczematous children. Several reports[37-39] have been made of cases of small epidemics of Kaposi's varicelliform eruption which clinically resembled eczema vaccinatum, but in which there was no history of vaccination or contact with a recently vaccinated individual. In these cases herpes simplex virus was found.

Barton and Brunsting of the Mayo Clinic reported two cases of Kaposi's varicelliform eruption associated with eczema in which the herpes virus was isolated. Their patients were adults. Kaposi's varicelliform eruption, as well as eczema vaccinatum, is attended with a high mortality rate. Among children less than 3 years of age it is more than 50 per cent.[40]

The diagnosis of accidental vaccination depends on the clinical history and certain laboratory findings. There should be a history of vaccinal contamination within a period of two or three weeks before the onset of symptoms. The lesion or lesions should resemble those of primary vaccinia and should pass from the papular to the vesicular and pustular stages. Biopsy of an individual lesion may show Guarnieri bodies. The Paul test is the most reliable laboratory procedure. Serologic methods for the determination of antibody formation against the vaccinia virus have been devised[41] but as yet they are impractical for general use.

Virus infections, particularly infection with the viruses of herpes simplex and vaccinia, are hazardous to eczematous individuals, especially children. The dangers of accidental vaccination must be kept in mind as an important untoward result of vaccination. Caution should always be taken to protect nonimmunized individuals, particularly eczematous infants, from becoming accidentally vaccinated from the vaccinal lesion of a recently vaccinated person.

SUMMARY

The two cases of accidental vaccinia presented in this paper consist of (1) a case of uncomplicated inoculation of the cheek of a child 18 months old and (2) a severe case of eczema vaccinatum in a child 6½ months old. Both children recovered. The complications of vaccination are many but occur infrequently. Probably the most common are benign exanthems and multiform eruptions. Accidental vaccinia may result from vaccination. One of the most serious complications of this is the development of eczema vaccinatum in an eczematous child. The relationship between eczema vaccinatum and Kaposi's varicelliform eruption is reviewed. The two cases reported indicate the dangers

of accidental vaccinia and make clear the need for protection to prevent the accidental vaccination of nonimmunized individuals by a recently vaccinated person.

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EVALUATION OF REPLACEMENT TRANSFUSION IN THE TREATMENT OF HEMOLYTIC DISEASE OF THE NEWBORN INFANT

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LATE in 1941 the clinical importance of the Rh factor in isoimmunization in pregnancy and sensitization by incompatible Rh transfusions was recognized, and it was established that hemolytic disease of the newborn infant (erythroblastosis fetalis) was the result of this antigen-antibody reaction. Since that time many of our best serologists have worked ardently on the subject, and it is due to their zeal that this complicated condition has been clarified in so short a time.

No subject could advance at such a pace without the evidence of differences of opinion. This is true of the serologic aspect of the subject, and today there are divergent views concerning the proper treatment of infants afflicted with hemolytic disease of the newborn.

For twenty-years I have treated icterus gravis by means of multiple transfusions.[1] During this period it became apparent that some of the infants were saved, but the severe cases died.

In 1942 when it became evident that the Rh factor was clinically important, we started using Rh-negative blood and multiple transfusions. As the subtypes of Rh were determined and the Hr setup recognized we used homozygous Rh-positive blood in transfusing these rare Hr cases. With this regime there was a definite improvement in our results, but there was still much left to be desired.

For the last two years we have been treating our patients with severe cases of hemolytic disease of the newborn infant by means of replacement transfusion.

The manner in which erythroblastosis manifests itself is often baffling. It is not always easy, even with meticulous history, perfect cooperation with the serologist, and careful physical examination, to make an early diagnosis or to evaluate just how severely affected a child may be and thus foretell the probable outcome. Undoubtedly, some cases are mild and the infants recover unrecognized. Some infants appear perfectly normal at birth or for the first twenty-four hours of life, and are dead of hemolytic disease in two to three days. Severe erythroblastosis, however, is often easily recognized at birth or shortly after, when it is seen that the baby is in grave trouble: the child may be convulsive or in shock, showing rapid, difficult respirations, weak cardiac action, petechiae and cyanosis, through which jaundice and probably anemia begin to appear. When the child is examined an enlarged but soft spleen and liver are found. The blood shows more or less erythroblastosis and anemia, and the red cells show sensitization which is demonstrated by their agglutination with normal compatible adult serum. The Witebsky-Rubin test is a very important aid in diagnosis,[2, 3] this agglutination phenomenon can also make the blood of these babies difficult to type, and because of this, it is probably safer to use 0 blood

Name

ERYTHROBLASTOSIS

No. 1, 3, 4, to be filled out by the Obstetrician

BUFFALO CHILDREN'S HOSPITAL

CHART SHOULD BE FILLED OUT WHEN ERYTHROBLASTOSIS IS SUSPECTED

1) History (With Dates)

Pregnancies

Miscarriages	Viable Births: Normal	Viable Births: Jaundiced	Total Pregnancies	Condition of Infant at Birth	Final Appraisal of Offspring

History of Transfusions

RH + or RH − Blood Used?

2) Blood Typing
R. H.
A. B. O.

Mother	Father	Wassermann	Siblings

3) Examination of Mother's Blood (Antibodies) with Dates

Date	Hour							

4) Birth (Leave Long Cord)

Date	Hour	Remarks Concerning Delivery, etc.

5) Cord Blood To Laboratory

Hg. Gms.	Type	RH	Erythroblasts Per 100 W.B.C.	Ict. Index	Antibody	Agglutination

6) Physical Examination of Baby (Frequently) During the First Few Days

Day and Hour	Jaundice	Cyanosis	Petechiae	Spleen	Liver	Lungs	Heart

7) Treatment
Replacement Transfusion
Blood Type Given

Type: Umbilical	Type: Saphenous	Time	Blood, C.C. Withdrawn	Blood C.C. Given

8) Results of Agglutination Tests Taken During Transfusion

Witebsky—Rubin Test	Coombs	RH	Condition Following Transfusion

9) Results

Date	Hg (Grm.)	Erythroblastic Count per 100 W.B.C.	Icteric Index	Physical Examination

Chart 1.

with added A B substance when transfusing patients with hemolytic disease of the newborn infant. A diagnosis or prognosis is not made on a single sign or symptom; account *must* be taken of the case as a whole.

Chart 1 is a sample chart for recording cases of erythroblastosis.

Many patients are dead at birth or are so severely affected that no known method of treatment can save them. In severe cases we believe early diagnosis and early replacement transfusion is the treatment of choice and will result in saving the lives of many who would otherwise be sacrificed. We do not believe in reserving this measure for cases in extremis; if this were done there could be no basis for comparison of treatments. Comparative statistics concerning treatment in erythroblastosis are at best difficult of evaluation.

Clinical classification of hemolytic disease of the newborn infant is difficult and there appears to be no connection between the type of antibody and the clinical manifestation of the disease. Occasionally there is no correlation between the serologic and hematologic findings and the clinical picture. We have seen severely affected babies born when the discernible antibodies in the mother were absent or low* and occasionally have seen high maternal antibodies and a child unscathed in spite of his being of susceptible Rh-positive type.

Because of these incongruities we believe that replacement transfusion should be done on the babies whose families have a history of marked sensitization and who are shown serologically and clinically to be suffering from hemolytic disease of the newborn infant.

A woman who is sensitized remains so, and when she has given birth to an erythroblastotic child practically all subsequent susceptible offspring will be affected in increasing severity. Chown's[4] report on a series of normal susceptible babies following the birth of erythroblastotic babies is the exception to the rule for which we have no explanation. We have observed such cases.

It has been stated that the evaluation of treatment should be based on a statistical study of 1,000 cases, treating alternate cases by means of either multiple transfusions or replacement transfusion. Who would have the audacity to institute such a regime or the longevity to complete such a statistical study? (A compilation of statistics from different clinics would not be satisfactory for comparison.) I would just as soon take 1,000 cases of appendicitis in childhood, operate on every other patient, then observe my results for science. Zuelzer, Wheeler, and Leonard[5] have endeavored to establish the severity of erythroblastosis by the evaluation of signs and symptoms and combinations of these. They have correctly pointed out that a diagnosis or prognosis cannot be made without a careful study of the case as a whole. This is a difficult assignment and because of the exceptions which occur, early estimation concerning the degree of sensitization and forecast of the clinical severity of the disease is sometimes impossible. It is important, however, in determining the kind of treatment to be used.

*The failure to find antibodies is not as common since the incomplete anti-Rh antibody was recognized, and there are probably antibodies still to be discovered. Antibody titer is best followed by saving the blood samples of the mother taken throughout pregnancy and comparing them at one examination toward the end of pregnancy. Slight differences in dilution and agglutination make a marked difference in antibody titer reading. (Witebsky.)

At present only the severe types of the disease are being referred to us for replacement transfusion. In 1947 we lost the first two patients out of a total ten cases. One died of a severe hemolysis due to overheated blood: the other was in extremis, dying during replacement; this infant had received a previous ordinary transfusion. Both of these cases were mistakes. Doing a replacement transfusion after ordinary transfusion always is hazardous and probably should not even be attempted. In the remaining eight cases, all severe, the infants recovered and today are alive and well and show no discernible neurologic sequelae.

During 1948 we have done replacement transfusions on sixteen patients and lost three; the three losses were last ditch attempts to save the lives of babies who were so severely damaged at birth as to preclude any kind of successful treatment. Thus in 1947 and 1948 we report a mortality of 19.2 per cent in our severe cases treated by replacement transfusion. We have broken down our mortality statistics and report on thirteen patients who were proved to have had erythroblastotic siblings; these patients treated by replacement transfusion showed a mortality of 15.3 per cent. This figure indicates the severity of the whole series treated by replacement, the mortality of the whole series being 19.2 per cent. We realize this is not a large series of cases from which to draw statistical evidence. All our fatal cases have been posted; the findings were those of severe erythroblastosis. There was no incidence of air embolism. One case showed massive cerebral hemorrhage.

Most of our cases treated by replacement transfusion are severely affected. As an example I quote the case of B.M.K. whose mother's history is as follows: She had a normal child born in 1941, a stillbirth in 1942, and in 1944 had an abortion at the third month. The mother was never transfused (abortions and transfusions play an important role in immunization). Bruce was the result of the fourth pregnancy, normal delivery. He was born on January 5, 1948, and was jaundiced at birth, cyanotic, had petechial hemorrhages, and was in shock. The mother was 0, Rh negative, the father 0, Rh positive subtype Rh_1 Rh_2. The baby's cord blood was Rh positive and showed the incomplete anti-Rh antibody in titer 1:128; the red cell agglutination with normal adult serum was strongly positive (4 plus). The icteric index was reported over 40, the Van den Bergh showed the prompt reaction 1.8 mg. per cent. The hemoglobin was 16 Gm., erythroblasts 42 per 100 leucocytes. The mother had anti-Rh saline agglutinins in her serum up to 1:2, and anti-Rh incomplete antibodies of at least 1:1024. The results of specimens taken during exchange transfusion were as follows: (1) agglutination of baby's cells in normal adult serum, positive up to the thirteenth specimen; (2) agglutination by anti-Rh serum on the slide, positive up to the fifteenth specimen; (3) Coomb's test strongly positive up to the fifteenth specimen, weak agglutination up to the 27th, and faint agglutination in the twenty-ninth specimen (29 specimens obtained). The report was by Dr. Ernest Witebsky. These tests are conclusive evidence of the completeness of the replacement.

In this case we were dealing with a severely sensitized child with high anti-Rh antibodies. The hemoglobin was not reduced and there was only a moderate

increase in erythroblasts. A 500 c.c. replacement transfusion was done. From our past experience it is difficult to believe that repeated transfusions without withdrawal and replacement could have possibly saved this baby's life. This type of treatment also avoids the danger of overloading the baby's circulation. The giving of too much fluid of any kind in these cases is a real hazard and extremely dangerous.

In our treatment of all cases of erythroblastosis we are very careful to correct existing dehydration, acidosis, hypoglycemia, hypocalcemia, hypoprothrombinemia, hypoproteinemia, anemia, and anoxia.

All of the early blood specimens withdrawn in our replacement transfusions fail to clot; this shows grave abnormality in the clotting mechanism in cases of erythroblastosis fetalis. The blood is far from normal in *every* respect. Dr. Diamond aptly puts it: "Are you going to drain the crank-case of bad oil and replace it, or are you merely going to add a little new oil to the old bad stuff?" In the evaluation of replacement transfusion it can be stated that to a great extent it helps to rid the infant's blood of offending anti-Rh antibodies. It replaces its red cells which cannot be functionally good with red cells which cannot be acted on by the antibody, and are good oxygen carriers. The exchange relieves anoxia and probably tends to minimize liver and brain damage. Because of the withdrawal, this procedure does not overload the circulation and this is important when the blood volume is not low. I have seen patients die with a high hemoglobin without dehydration; this, however, is the exception.

Replacement transfusion has been done by various men[6, 7, 8, 9, 10, 11, 12, 13, 14] using different techniques. We use the umbilical vein method as described by Louis K. Diamond; this method should be used only the first twelve hours of life; at times the vein may be patent after twelve hours, but if used later there is the danger of disengaging clot and causing embolism. In replacement transfusion the giving of blood is easy; the difficulty is the withdrawal. Wallerstein[7, 8] used the longitudinal sinus for withdrawal and Wiener[10, 11, 13] withdraws from the radial artery using heparin.

Because of the bleeding tendency and poor clotting power of the blood in erythroblastosis fetalis, we believe the use of heparin in the child's circulation is not without danger.

When we do not use the umbilical vein, we withdraw and replace through the saphena magna vein using polyethylene tubing, gauge 18 and 19; these plastic catheters were developed by Dr. Franc Ingraham and used in umbilical vein replacement by Dr. Louis K. Diamond. The technique of the saphenous method is not difficult, it is neat and expeditious, and heparin is unnecessary. We prefer this technique.

Replacement transfusion is not radical treatment; it is conservative and, when properly done, holds practically no hazard. We have never had a case of air embolism. With proper technique this should not occur. Any kind of treatment or no treatment at all is hazardous in moribund or neglected cases of hemolytic disease of the newborn infant. In a last-minute effort to save a life, infants have died on the way to the operating room or shortly after starting

replacement. However, enough severe cases are saved to warrant doing a replacement transfusion and thus giving the baby a chance for life even though such a regime plays havoc with statistics.

In conclusion, it is readily seen that in handling cases of hemolytic disease of the newborn infant it takes good judgment based on fact in order to arrive at an early diagnosis resulting in effective early treatment.

Having used the various described treatments throughout the years, and having observed to date the concomitant use of the other methods, we have come to the conclusion that all severe cases of erythroblastosis fetalis should be treated by replacement transfusion. Only the mild cases can be temporized with, and some of the apparently mild cases turn out to be severe enough to cause death or result in brain damage. In case of doubt as to the severity of the immunization, we believe the baby should be given the benefit of the doubt and receive replacement. We are watching with interest the development of hapten or some other agent to prevent the deleterious action of antibody on the fetus and child.

This is not an exact controlled, statistical study. I do not believe this condition lends itself to such a statistical approach. This is, however, a study based on a twenty-two year observation of many cases of hemolytic disease of the newborn infant.

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TICK PARALYSIS IN THE EASTERN UNITED STATES

A Summary, With Report of Four New Cases From Georgia

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INTRODUCTION

FOR many years tick paralysis has been recognized in the Canadian and American northwest, but only in the past decade have case reports begun to appear from the eastern United States. Though uncommon, the disease is important since it may be confused with poliomyelitis and, if unrecognized, may be fatal. The diagnosis is often readily confirmed by finding an engorging tick and by prompt recovery of the patient after its removal.

In the summer of 1948 four patients with tick paralysis were observed at Grady Memorial Hospital. These cases are being reported to emphasize an unfamiliar hazard in the eastern United States. Reference is also made to fourteen other published cases which have occurred east of the Mississippi River. Only a brief description of the disease is included since two excellent reviews[1, 2] are available.

CASE REPORTS

Case 1.—*History:* B. D., a 3-year-old white farm girl from Hazlehurst, Ga., was admitted May 13, 1948. She was well until two days before admission when she had three loose stools. Next day she got up in the morning but soon returned to bed. A little later she was unable to walk. She could move all extremities, but fell on attempting to stand. In the afternoon she became unable to sit up or raise her head. During the night she was irritable and hypersensitive, screaming when touched. The legs were weak and the right arm paralyzed. On the morning of admission she could still move the legs and left arm slightly. Her speech was indistinct and she choked on attempting to swallow. The choking became worse and breathing difficult. She lost consciousness just before entering the hospital at 3:00 P.M.

Physical Examination: The child appeared moribund. She was limp, comatose, drooling, and choking on pharyngeal secretions. The rectal temperature was 98.2° F., pulse 130, respirations 28. Breathing was shallow and diaphragmatic. The limbs were flaccid and motionless. Tendon and abdominal reflexes were not obtainable. There was little if any stiffness of the neck. Slight lateral nystagmoid movements of the eyes were noted. The nose and pharynx contained mucoid secretions, and the gag reflex was absent. A search of the scalp and body for ticks revealed none.

Course: The nose and pharynx were aspirated frequently, the foot of the bed elevated, and the head turned to the side. Oxygen was given nasally. Penicillin was administered intramuscularly, 40,000 units every six hours. Parenteral fluids were given. By 6:00 P.M. consciousness had returned and the speech, though thick and nasal, was comprehensible. During the night she could move all extremities, but there was marked weakness. She was unable to turn in bed, and when lifted the head fell back limply. The respirations

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became deeper and easier. On May 14 she could move her limbs better but the neck muscles were still weak. The knee jerks were present. Speech was normal and pharyngeal secretions gradually ceased accumulating. On May 15 the gag reflex had returned and she could take fluids by mouth. The respiration was normal and she was able to sit up. Weakness of the hands and neck flexors was still noted, but gradually subsided. All motor power quickly returned. On May 16 she was walking about in bed, and by May 17 recovery was complete.

There was no fever. No sensory loss was detected. Except for incontinence of urine during the first twenty-four hours of hospitalization, the bladder and bowel functioned normally throughout. The child was well when discharged on May 20.

Pertinent Laboratory Data: On admission the leucocyte count was 13,280 with 81 per cent polymorphonuclears, 16 per cent lymphocytes, 2 per cent monocytes, and 1 per cent eosinophiles. The Kahn test was negative. Lumbar puncture on May 14 revealed clear fluid containing 4 lymphocytes per cubic millimeter, with 14 mg. of protein and 62 mg. of sugar per hundred cubic centimeters. The Pandy test was negative, and there was no growth on culture.

Comment: The initial impression was poliomyelitis. However, the absence of fever, the minimal stiffness of the neck, and the normal spinal fluid, combined with the extraordinarily rapid recovery, seemed to weigh against this diagnosis. The nature of the disease remained a mystery until the parents came to take the child home. It was then learned that on May 13 an engorged tick had been found attached to the scalp above and behind the right ear. It was removed by the parents at about noon, three hours before admission. This information, together with the typical clinical picture, established the diagnosis of tick paralysis.

The tick removed from the patient was not preserved, but several days later the father sent us six ticks collected from dogs at the child's home. These were identified as females of *Dermacentor variabilis*. One was unengorged and five were in various stages of engorgement. Some of them deposited large numbers of ova.

CASE 2.—*History:* V. C., a 4-year-old white girl also from Hazlehurst, Ga., but living some miles away from the patient of Case 1, was brought to the Emergency Room May 28, 1948, because of difficulty in walking. She was well until the morning of May 27 when she showed poor control of her legs and an unsteady gait. This improved somewhat toward evening but was worse on the morning of May 28. There was marked weakness and ataxia of the legs. The child was unable to walk without support, but paralysis was never complete. At 9:00 A.M. the parents found and removed two ticks, one large and one small, which were attached to the scalp in the right occipital region. On arriving at the hospital about 7:30 P.M. she had already improved considerably. There had been no fever.

Physical Examination: The child was alert and could walk, although the gait was unsteady with a wide base. The rectal temperature was 99.2° F. There was no stiffness of the neck or back. The cranial nerves were normal. All extremities could be moved, and there was little or no detectable muscle weakness. The upper abdominal reflexes were present, the lower ones were not obtained. Knee jerks were absent. Ankle jerks were present and equal. Bite marks were visible on the scalp where the ticks had been attached.

Comment: A diagnosis of tick paralysis was made from the history and the finding of ataxia of the legs with absent patellar and lower abdominal reflexes. The parents were allowed to take the child home without further treatment.

CASE 3.—*History:* F. D., a 6-year-old Negro girl from Lexington, Ga., was admitted to the hospital June 15, 1948, because of difficulty in walking. She

was well until the evening of June 12 when she seemed "feverish." On the morning of June 13 she was "weak in the knees" and could not walk. She complained of "stomach-ache" and had three loose bowel movements. Later in the day the gait was unsteady but she was able to walk about by holding on to objects. On June 14 the legs were still weak though not entirely paralyzed. She could not climb onto her tricycle, but was able to pedal it when placed on the seat. She fell on attempting to get off. At 11:00 A.M. she was seen by a physician who found her unable to stand and suspected poliomyelitis. She was admitted to the hospital at 11:00 A.M. June 15. Meantime some improvement had occurred.

Physical Examination: The child did not appear acutely ill. The rectal temperature was 100° F. She was able to stand alone, but the Romberg test was positive. She could walk with an unsteady gait on a wide base. There was no grossly detectable weakness of the extremities, but the knee and ankle jerks were absent. The plantar responses were flexor. Tendon reflexes in the arms were brisk and abdominal reflexes were normal. The neck was supple, Kernig's sign negative. A partially engorged tick was found attached to the scalp in the left temporal region. It was removed at 12:30 P.M. June 15.

Course: By the morning of June 16, twenty-two hours after removal of the tick, the child's gait had improved but was still slightly ataxic. The Romberg sign was negative. The left ankle jerk was obtainable with reinforcement. The right ankle jerk and both knee jerks remained absent. On June 17 the gait was normal. The left ankle jerk was easily obtained, the right was weakly present with reinforcement and improved slightly by the next day. On discharge June 18, the child appeared well but the knee jerks were still absent and the right ankle jerk was weaker than the left. There was no fever during hospitalization.

Pertinent Laboratory Data: On admission the leucocyte count was 9,200 per cubic millimeter with 52 per cent polymorphonuclears, 46 per cent lymphocytes, and 2 per cent monocytes. The Kahn test was negative. Lumbar puncture yielded a clear colorless fluid containing 1 leucocyte per cubic millimeter, with protein 12 mg. and sugar 56 mg. per hundred cubic centimeters. No growth was obtained on culture of the fluid. The tick was identified as a female of *D. variabilis*. Several days after removal it deposited a large number of ova.

CASE 4.—*History:* C. H., a 2-year-old white boy from Monroe, Ga., was brought to the hospital July 3, 1948, because of difficulty in walking. He was well until two days before admission when he became irritable and began walking "as though drunk." He cried whenever his legs were moved and preferred to lie quietly. Next day the legs were weaker; he was still able to stand and walk a few steps although use of the legs seemed painful. A physician found the temperature to be 101° F. rectally, suspected poliomyelitis, and the boy was admitted to the hospital at 9:00 P.M. July 3.

Physical Examination: The child was husky, with long curly hair. He resented being disturbed and screamed loudly during the examination. It was impossible to tell whether this was due to pain or apprehension. There was no stiffness of the neck. Kernig's sign was negative. Cranial nerves and upper extremities were normal. Generalized weakness of the legs was noted, without complete paralysis of any muscles. The child could stand alone, though weak and wobbly; the gait was unsteady with a wide base. The Romberg sign was positive. Biceps, triceps, and abdominal reflexes were present and equal bilaterally. Knee and ankle jerks were absent. The plantar responses were normal. Sensory examination was unsatisfactory but revealed no anesthesia. A partially engorged tick was found attached to the scalp in the occipital region, and removed.

Course: On July 4, twelve hours after removal of the tick, the child was much less irritable. He sat up well but the Romberg sign was still positive. The gait continued to be jerky and unsteady with a wide base. He cried while walking as though in pain. Knee jerks were present. On this day (one of the hottest of the summer with air temperature nearly 100° F.), he took fluids poorly and his rectal temperature rose to 101° F. There was no evidence of infection. On July 5, thirty-six hours after the tick's removal, some diffuse weakness of the legs remained. All tendon reflexes were present, equal, and hyperactive. The maximum rectal temperature was 100.2° F. On July 7, three and one-half days after removal of the tick, the child did not yet walk willingly. His gait, though improving, was still unsteady with a moderately wide base. Upon the insistence of his parents he was discharged from the hospital July 7. A physician later wrote that recovery was complete.

Pertinent Laboratory Data: The blood leucocyte count on July 4 was 15,200 with 53 per cent polymorphonuclears, 44 per cent lymphocytes, 1 per cent monocytes, and 2 per cent eosinophiles. On July 5 the leucocyte count was 12,100. The Kahn test was negative. Lumbar puncture on admission revealed clear fluid containing 2 lymphocytes per cubic millimeter, with 20 mg. of protein and 68 mg. of sugar per hundred cubic millimeters. Pandy test on the spinal fluid was negative, and culture yielded no growth. The tick removed from the patient was identified as a female of *D. variabilis.*

ETIOLOGY

Various species of Ixodidae or hard ticks have been reported to cause paralysis. The Argasidae or soft ticks have not been implicated. While engorging on its victim, the tick apparently injects a neurotoxin. This toxic agent is thought to act upon the spinal cord and bulbar nuclei,[3] causing incoordination, weakness, and paralysis. Evidently it is rapidly destroyed or excreted, for when the tick is removed the nerve cells regain normal function.

Tick paralysis has been produced in experimental animals only with gravid female ticks, and this observation led to the theory that the toxin was elaborated by the ova. While various toxic extracts have been prepared from tick eggs, the toxin causing paralysis in naturally occurring cases has not yet been definitely identified.[4-6]

It appears that the tick must feed for several days before symptoms develop. Paralysis has occurred in infants after a tick has engorged for four days, and various studies indicate that large amounts of toxin are injected on the fifth and sixth days.[1] Female ticks may feed on a suitable host for periods ranging from four to ten days or more, usually seven to nine. Paralysis becomes evident in experimental animals after five to seven days of engorgement.[3, 7, 8] Male ixodid ticks engorge to a lesser degree and feed for a shorter period. It has been suggested[1a] that this may explain why the female is more effective in producing paralysis. At least one case is on record, however, of paralysis caused by a male *D. andersoni.*[9] The tick was attached in the axilla of an adult, causing partial paralysis of the arm on the same side. This cleared within twelve hours after the tick's removal.

Since the salivary glands of ticks enlarge enormously while feeding, it has been postulated[3] that the toxin is present in the saliva and is introduced into the host in increasing amounts during the final stages of engorgement. Tick salivary glands were injected into animals with unconvincing results. Other

workers[10] were unable to produce paralysis with salivary gland extracts. In some human cases paralysis has continued to progress despite removal of the tick and improvement did not begin until broken-off mouthparts were excised.[10, 11] Such instances suggest that the mouthparts contain a high concentration of toxin. The nature of the toxin is still unknown. It is not clear whether it is formed in the salivary glands, or whether the saliva simply transmits or perhaps also activates a toxin formed in the ova or elsewhere.

CLINICAL PICTURE, TREATMENT, AND PROGNOSIS

Most human cases occur in children, especially in young girls. The tick is usually attached to the scalp and hidden by the hair. Both white and Negro races are susceptible.

Irritability may be noted twenty-four hours before appearance of motor symptoms. Mild diarrhea may occur. Often the first alarming symptoms appear in the morning when on arising the child shows weakness and poor control of the legs, staggering, and falling. Sensory changes are usually absent, but there may be hyperesthesia and paresthesia in the affected extremities. Flaccid paralysis soon develops and ascends in one or more days to involve the trunk, arms, neck, tongue, and pharynx. Tendon reflexes are diminished or absent. If the trunk is affected the abdominal reflexes are also unobtainable. There is little or no stiffness of the neck and back. With the appearance of bulbar involvement the voice becomes thick and nasal; the child is unable to swallow and chokes on pharyngeal secretions. Nystagmus and strabismus are sometimes noted, and in infants terminal convulsions may occur. The respirations become abdominal in type, shallow, rapid, and finally irregular. Restlessness gives way to stupor and death results from paralysis of the respiratory muscles or from respiratory obstruction by aspirated material.

The temperature seldom exceeds 100° F. unless there is a secondary infection. The leucocyte count is usually normal, although a leucocytosis of 10,000 to 17,000 cells per cubic millimeter is occasionally observed.[12-15; see also Cases 1 and 4] The spinal fluid is almost always normal. The erythrocyte count, hemoglobin, and urine show no changes.

If the tick is removed before appearance of bulbar signs, the paralysis subsides and recovery is complete within a few days. Milder cases may be quite well within twenty-four hours. Nevertheless all patients should be observed carefully until recovery is well under way, because if other ticks or retained mouthparts have been overlooked the paralysis may progress. When bulbar or respiratory paralysis develops, death may occur if the tick is not removed in time.

The tick is usually located on the scalp or neck, but may be attached to any part of the body, especially the ear, axilla, groin, vulva, or popliteal space. It should be removed immediately, with care to avoid breaking off the mouthparts and allowing them to remain embedded in the skin. Mouthparts which have been retained should promptly be excised. The whole body surface should be searched for other ticks.

In advanced cases respiratory and bulbar paralysis dominate the picture. If the patient cannot swallow and is choking on pharyngeal secretions, the

foot of the bed should be elevated and the head turned to the side to promote postural drainage. Frequent aspiration of the pharynx should be performed. Nothing should be given by mouth until the patient is able to swallow normally. Parenteral fluids are indicated. Sedatives and narcotics should be avoided. Penicillin, given parenterally, is useful in combating aspiration pneumonia. Oxygen should be given. When paralysis of the diaphragm and intercostal muscles is present, a respirator may be life saving.[15-17] If no respirator is available other methods of artificial respiration should be tried. Unfortunately, bulbar and respiratory involvement usually co-exist. Patients with puddling of pharyngeal secretions should not be placed in a respirator unless actually unable to breathe; there is too much danger of aspiration into the tracheobronchial tree. An apparently moribund patient may show striking improvement in respiration within a few hours after removal of the tick.

HISTORY AND GEOGRAPHICAL DISTRIBUTION

Tick paralysis in man and animals was first mentioned in Australia more than a hundred years ago. In 1904 it was described as affecting sheep in South Africa. Later cows, horses, rabbits, guinea pigs, dogs, cats, and other animals have been found susceptible. The disease is commonest in the young of the various species; older animals appear to be relatively resistant. The first human cases in North America were reported from British Columbia in 1912, followed shortly by others from Oregon and Idaho. Since then the disease has been recognized in Crete and Jugoslavia, and many additional cases have been published from the northwestern United States and western Canada. The first cases from the eastern states were reported from South Carolina[18] and Georgia[19] in 1938.

In the northwestern United States and adjoining portion of Canada the wood tick, *Dermacentor andersoni Stiles,* is usually responsible. The distribution of cases corresponds with the northern part of the range of this tick including British Columbia, Alberta, Washington, Oregon, Idaho, Montana, Wyoming, and Colorado. No reports have yet appeared from California, Nevada, and Utah where *D. andersoni* is also prevalent, nor from North and South Dakota, Kansas, Arizona, and New Mexico which are on the fringes of its known range.[20] A unique case from British Columbia was attributed to the bird tick *Haemaphysalis cinnabarina.*[21]

In the eastern United States the dog tick, *Dermacentor variabilis Say,* has been responsible for paralysis in cases where positive identification of the tick was made.[12, 14, 16, 19, 22-24] Reports from South Carolina[13] and Washington, D. C.[25] of finding *D. andersoni* on patients with tick paralysis are subject to question since *D. andersoni* is not known to occur in the East. On the other hand, *D. variabilis* is widely distributed over the eastern United States as far west as Texas, Oklahoma, and Nebraska, and is also prevalent in California.[20]

Since 1938 three cases of tick paralysis have been reported from Georgia[19, 22, 26] and three from South Carolina[12, 13, 18] followed by single cases from North Carolina,[27] New York,[23] and the District of Columbia,[25] two from Kentucky,[14] and three from Virginia.[16] In all, fourteen cases occurring east

of the Mississippi River have been published, and one from Texas.[24] As yet the disease has not been reported from New England. Additional cases might be expected throughout the range of *D. variabilis*.

DISCUSSION

The Grady Memorial Hospital serves as a referral center for poliomyelitis, and all of our cases arrived with that diagnosis. McCue, Stone, and Sutton,[16] in a similar center at Richmond, Va., saw three patients with tick paralysis referred as poliomyelitis. This was also the initial diagnosis in many other reported tick paralysis cases. The seasonal incidence of both conditions contributes to this confusion. Tick paralysis occurs in warm weather when ticks are active, and when poliomyelitis is also likely to be prevalent. The twelve eastern cases for which date of onset is available and our four cases occurred in the following months: 1 in March, 2 in May, 6 in June, 6 in July, and 1 in August. It is especially important that those who treat acute poliomyelitis be aware of the possibility of tick paralysis since early diagnosis and tick removal may save patients who would otherwise die with a mistaken diagnosis of bulbar poliomyelitis.

Several features of tick paralysis are helpful in differentiating it from poliomyelitis. Usually there is no fever, and the spinal fluid is normal. Muscle spasm is absent, and there is little or no stiffness of the back and neck. Marked ataxia often precedes paralysis by several hours or even days, first in the legs, then in the arms. Ascending involvement is particularly suggestive of tick paralysis, while progression of paralysis without fever is uncommon in poliomyelitis. The muscular weakness in typical cases is diffuse and bilateral. It is usually but not necessarily symmetrical. Generally there is equal involvement of the legs, but sometimes[23, also Case 3] the tendon reflexes return more rapidly on one side than on the other. In Case 1 the right arm was apparently paralyzed sooner and more severely than the left. In two of our patients the ankle jerks returned before the knee jerks after tick removal.

Other conditions which may be considered in differential diagnosis are polyneuritis, myelitis, infectious neuronitis (Guillain-Barré syndrome), syringomyelia, and spinal cord tumor. Such diagnoses can be dismissed when a tick is found and prompt recovery follows its removal. Furthermore these conditions usually show characteristic sensory involvement. Although hyperesthesia and paresthesia may be present in the early stages of tick paralysis,[18, 28, also Cases 1 and 4] diminution or loss of skin sensation rarely if ever occurs.

Interesting clinical variations of tick paralysis may be encountered. Patients seen early may show only incoordination and absent tendon reflexes in the legs, with weakness but no complete paralysis. If the tick is removed in this stage, true flaccid paralysis may never develop (Cases 2, 3, and 4). Even with bulbar involvement the extremities may not be completely paralyzed.[16, also Case 1] Especially treacherous is the tendency toward temporary improvement in the early phases.[12, 15, 16, 23, also Cases 2 and 3] This may be followed abruptly by severe ascending paralysis.

The speed with which progression occurs varies widely. The patient of one reported case[27] showed symptoms for only two days before removal of the tick, but died of respiratory paralysis. This was the only fatal outcome in the eighteen eastern cases. In contrast, the duration of symptoms before tick removal was reported to be nine days in a case with bulbar involvement,[14] and ten days in another case with marked ataxia but no paralysis or bulbar signs.[23] Both these patients recovered.

Stanbury and Huyck[2] cite the greater severity of the Australian disease in which the height of paralysis may not be reached for forty-eight hours after removal of the tick, and recovery may require weeks. Local paralysis has been reported in cases[29, 30] where the tick was attached in the external auditory canal with homolateral facial paralysis. Also described[17] are ptosis of the brow and eyelid with a tick attached to the temple, and partial paralysis of the arm with a tick in the axilla. A similar case was reported from Alberta.[9] The factors which determine whether the paralysis is local or of the ascending type are not known.

Many fundamental questions about tick paralysis remain to be answered. The exact nature of the toxin and its mode of action have not been established. Satisfactory pathological studies on naturally occurring human or animal cases are lacking. A number of explanations have been offered to explain the apparent predilection for the young. Adults may be less likely to acquire ticks than children and more likely to remove them promptly. It is also possible that some immunity to the attachment of ticks may develop as a result of repeated exposures.[31] The theory that the greater size of the adult dilutes the toxin below the symptomatic level is not convincing in the light of authentic reports of cases in full-grown individuals.[10, 18, 28] The finding of the tick on the head or neck in the vast majority of patients is of interest. In all eighteen eastern cases the tick was attached to the scalp. Whether this is only because the tick is more likely to escape notice when hidden in the hair, or whether the toxin may more rapidly and effectively reach the central nervous system from such locations, is unknown.

The relative paucity of reported tick paralysis cases in the United States is puzzling in view of the wide distribution of *D. andersoni* and *D. variabilis*, and considering the large number of children bitten. Reporting is doubtless incomplete, although the dramatic nature of the disease invites publication. Perhaps some cases may be misdiagnosed as poliomyelitis. Surely many cases are prevented by removal of the tick before symptoms develop. Others may unknowingly be cured by tick removal when illness prompts careful examination, or possibly the tick may drop from the victim spontaneously. In the dog, recovery can occur while the tick remains attached.[8] It is not known whether this can happen in human patients. The incidence of tick paralysis may also be influenced by the fact, observed in animal experiments, that not all ticks of incriminated species cause paralysis, even though the host is susceptible.[3] It is not clear whether some engorging ticks fail to produce toxin or whether unknown factors interfere with its effect upon the host.

Thus far no cases of tick paralysis have been attributed to *Amblyomma americanum*. This tick heavily infests large areas of the southern and south-

eastern states and has recently been found, like *D. andersoni* and *D. variabilis*, to serve as a vector of spotted fever and tularemia.

SUMMARY

1. A résumé of some known facts and unanswered questions about tick paralysis is presented.

2. Reference is made to fourteen cases previously published from the eastern United States.

3. Four new cases from Georgia are reported, from two of which *D. variabilis* was identified.

4. It is suggested that additional cases may be expected throughout the range of *D. variabilis*.

5. Tick paralysis is likely to be confused with poliomyelitis. The differential diagnosis is discussed.

The assistance of the Pediatrics staff is gratefully acknowledged. Dr. E. C. Cale and Dr. Morris Price obtained ticks from two of the patients. All tick identifications were made by Dr. Harry D. Pratt of the United States Public Health Service.

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FAVISM

Report of a Case in a Child

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THE fava bean *(Vicia fava)* is a common food in the diet of most of the Italian families in Buffalo, N. Y. A survey of fifty Italian children entering our outpatient department revealed that this legume is eaten by 80 per cent of their families. Usually the beans are boiled and served with other vegetables. Occasionally they are eaten raw. Physically the fava bean resembles the lima bean except that it is twice its size. In this country the plant is cultivated particularly in communities with a large Italian population. In western New York State the fava bean is grown in the Eden Valley and Niagara County areas. New Jersey, Illinois, Louisiana, Florida, Mississippi, California, and the New England states also harvest large crops of fava beans. Reports from nearly all of these areas cite the seasonal incidence of favism coincident with the blossoming of the fava plant during the spring and summer.

CASE REPORT

C. L., an Italian male child of 4 years, was brought to the Outpatient Department of the Children's Hospital of Buffalo on July 21, 1947, with a complaint of jaundice for two days. Three days before admission, while playing in the kitchen with another child, the patient ate two raw fava beans, as did the other child. The patient was again given a small portion of cooked beans for supper. The next afternoon his mother noticed that his urine was dark orange-red colored. He voided about four times that day and the urine discoloration persisted. The boy had no complaints otherwise. The following morning his eyes appeared yellow and the abnormal urine color persisted. The child played about the house but refused his lunch. His appetite remained poor. By the next morning his jaundice had progressed to involve the skin of his body. On his way to the clinic he vomited once. His playmate did not develop any of these symptoms. The patient had no fever, chills, or convulsions. His stools were not unusual in number, consistency, or color.

Prior to this illness the patient had had several episodes of upper respiratory infections, otitis media occurring twice. The ear infections quickly responded to medication with sulfadiazine and penicillin. On one occasion following the administration of penicillin, he developed scattered eruptions over his body which the mother believed were hives. The patient's health for the previous six to seven months had been good. His birth, developmental, and feeding history were essentially negative except for an inadequate intake of vitamin D. The patient's father was born in this country, and his mother in Sicily. The parents denied the presence of asthma, eczema, hives, or other allergic manifestations in the family. The patient had one older female sibling who was in good health. Fava beans were frequently eaten raw as well as cooked by the entire family without resulting complaints. The child's paternal grandmother

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TABLE I, *A*. LABORATORY STUDIES

	DAYS AFTER ONSET												
	3	4	5	6	7	8	9	10	11	15	22	48	146
Hemoglobin (Sahli) Gm. per 100 c.c.	5.4	6.5	—	7	7	8	9	10	10.5	12	12	13.5	12
Red blood cells (per cu. mm.) millions	2.1	2.38	—	—	—	—	—	—	3.5	—	—	4.3	—
Nucleated red blood cells per 100 white blood cells	3	0	—	—	—	—	—	—	0	—	—	—	—
Reticulocytes (%)	—	9.1	—	—	—	—	—	—	—	—	1.4	—	—
White blood cells (per cu. mm.)	16,000	8,900	—	7,500	—	—	—	6,200	—	400	7,400	4,000	6,850
Differential (%)													
Bands	15	1	—	—	—	—	—	0	—	5	10	2	3
Filaments	40	56	—	—	—	—	—	32	—	38	50	40	41
Lymphocytes	40	35	—	—	—	—	—	68	—	47	36	54	51
Monocytes	5	1	—	—	—	—	—	0	—	4	3	0	0
Eosinophiles	0	0	—	—	—	—	—	0	—	6	1	4	3
Basophiles	0	4	—	—	—	—	—	0	—	0	0	0	0
Platelets (per cu. mm.)	319,000	—	—	—	—	—	—	—	—	—	—	—	—
Hematocrit	22	22	—	—	—	—	—	31	—	—	—	—	—
Icteric index (units)	100+	—	—	5-7+	—	—	—	—	—	—	—	—	—
Serum bilirubin (mg. %)	2.96	—	—	0.23	—	—	—	—	—	—	—	—	—
Reaction	Indirect	—	—	Indirect	—	—	—	—	—	—	—	—	—
Sedimentation rate (mm./hr.)	44	—	—	—	—	—	—	13	—	—	—	—	—
Urine													
Albumin	1+	0	0	0	0	0	0	0	—	0	0	—	0
Urobilinogen 1/20 dil. (qual.)	4+	3+	1+	0	0	0	0	0	—	0	0	—	0
Stool													
Urobilinogen excretion (qual.)	4+	4+	—	—	—	—	—	1+	—	—	—	—	—

TABLE I, *B*. LABORATORY STUDIES

THIRD DAY AFTER ONSET			
Blood culture		Sterile	
Blood (Kahn)		Negative	
Cephalin flocculation		Negative	
Donath-Landsteiner hemolysin test	12 H. 0° C.	Negative	
	12 H. 37° C.	Negative	
Cold agglutination		Negative	
Blood chlorides		108 meq.*	
Blood N.P.N.		38 mg. %	
Blood CO_2 combining power		27 meq.	
Fragility			
Hemolysis—Patient and Control	Began 0.38		
	Complete 0.32		
Bleeding time		3 minutes	
Clotting time		5 minutes	
Clot retraction		1 hour	
Tourniquet test		Negative	
Bone marrow†			
Total nucleated R.B.C.		85,000	
Differential %			
Myelocytes (M)	5	Monocytes	0.5
Myelocytes (E)	1.5	Plasma cells	0.5
Juveniles	24.0	Disint. cells	6.0
Bands	12.0	Normoblasts (B)	9.5
Filaments	9	Normoblast (P)	6.5
Eosinophils	2.5	Normoblast (O)	8.0
Lymphocytes	11.5	Megakaryocytes per 50 l.p.f.	20/50
Interpretation: Myeloid and erythroid hyperplasia.			

*Milliequivalents.

†Performed five days after onset.

had had several attacks of jaundice and apparently hemoglobinuria after eating fava beans. These attacks had occurred while living in Palermo, Italy, as well as in this country. On one occasion she had become jaundiced after walking near a field of the flowering fava plant. It was also stated that her small infant daughter died shortly after eating a meal of fava beans.

Examination revealed an alert, cooperative, Italian male child of 4 years. He was moderately icteric and the mucous membranes were pale. There was neither dyspnea nor cyanosis. He had a generalized lymphadenopathy consisting of nontender nodes 1 to 2 cm. in diameter. The heart rate was 120 per minute, and a grade II, low-pitched, blowing, apical systolic murmur was heard over the precordium. There was no cardiac enlargement and the blood pressure was 118/50. The liver and spleen could not be palpated, and there was no costovertebral tenderness. Several ecchymotic areas 2 to 3 cm. in size, presumably due to trauma, were found over the anterior aspects of both shins. The remainder of the examination was negative.

The course in the hospital was uneventful. On the second day after admission the patient's liver was found to be enlarged and extended 2.5 cm. below the costal margin but was not tender. There were no complaints. He played in his crib, ate his meals, and took an adequate amount of fluid. On the ninth hospital day he was discharged to his home to be followed in the Outpatient Department of the Children's Hospital. At the time of discharge jaundice was no longer apparent, the precordial murmur had disappeared, and the liver edge was just palpable below the costal margin. No treatment had been given other than ferrous sulfate by mouth.

The laboratory findings have been charted in Table I. On admission there was a severe anemia with stippled and nucleated red cells showing anisocytosis

and polychromatophilia, and the blood showed a reticulocytosis. The white blood count showed no significant change. The icteric index and serum bilirubin were elevated, and the urobilinogen excretion in the urine and stool was increased. Albuminuria without hemoglobinuria was also present. By the time of discharge his hematologic picture was within the normal range and has remained so over a five-month period of observation. Immunologic and other special studies were undertaken to elucidate the mechanism of the hemolytic anemia.

DISCUSSION

Asymptomatic jaundice occurs frequently in the first decade of life. When present in a previously healthy Italian child, erythroblastic anemia, hepatitis, leucemia, or a hemolytic anemia are considered among the most probable diagnoses. However, the diagnosis of favism can be made quickly from the history alone.

Luisada[1] has recently reviewed the hemolytic syndrome of favism as it occurs in Italy and this country. Approximately seven cases* have been reported in the American literature, two of which occurred in children.[2] The symptomotology varies from mild, painless jaundice and pallor to profound vasomotor collapse with convulsions and hemoglobinuria. Gastrointestinal complaints are believed to be more common in children. Malaise, weakness, dyspnea, and fatigue, when present, represent manifestations of the anemia. Jaundice and pallor are constant physical findings. Other signs will depend upon how soon the patient is seen after the hemolytic crisis. Hepatomegaly, splenomegaly, and cardiac murmurs may be present by the second day, particularly in children. The usual laboratory findings are those consistent with an acute hemolytic anemia. Special hematologic studies such as acid, heat, and mechanical fragility, bleeding and clot retraction time, the Donath-Landsteiner and cold agglutination tests are negative.

From the investigations of the Italian workers favism was believed to be a manifestation of sensitivity to the fava bean. Using extracts of the fava bean for skin testing, sensitivity was demonstrated in those patients subject to this hemolytic syndrome. Passive transfer experiments also corroborated this apparent reactivity to the fava bean protein. The severity of the symptoms of favism probably is not dependent upon the amount of bean ingested, for the disease can occur following inhalation of the pollen of the flowering plant, or even in suckling infants through the mother's milk. The work of Pazzi,[3] Lotti,[4] and Parlato[5] suggests that the antigen contained in the fava plant is a complex protein, sensitization occurring to the various fractions of the protein. During an attack skin tests and passive transfer experiments with the fava bean antigen are consistently negative. However, using other parts of the plant one may still show the patient to be sensitive to the protein fractions of the fava bean. Following recovery the patient will demonstrate positive skin tests and passive transfer antibodies to the original allergen which caused the hemolytic anemia. Pesci[6] believed that the hemolytic anemia was brought about by an anaphylactoid state, the bean protein acting directly upon the red cell to cause hemolysis. This

*Since this paper was written, an additional case of favism occurring in a 5-year-old male child of Italian descent was reported. Rosen, A. P., and Scanlan, J. J.: New England J. Med. 239: 367, 1948.

work has never been substantiated. Similarly the toxic (an alimentary toxin by-product) and the parasitic or infectious theories held to be responsible for the hemolytic process have been discarded. The immunologic studies in the American literature have been limited to skin-testing the patient with extracts of the fava bean. In only two of the four patients on whom this test was performed was there a positive intradermal reaction. Two other patients were refed the fava bean after they had recovered from the hemolytic anemia, and both had a mild recurrence of their symptoms.

In conjunction with the observations made on our patient, an attempt was made to study the toxic properties of the fava bean upon the red cell as well as the antibody response of the patient. These experiments were carried out over a five-month period. A concentrated extract was prepared from the bean after removal from the pod. The nitrogen unit was determined by the phosphotungstic acid nitrogen method.

Intradermal injection of one cubic centimeter of the concentrated extract into a rabbit failed to demonstrate any toxicity either locally or systemically. No evidence of hemolysis or agglutination of the human red cell by the fava bean extract could be found. Serial dilutions of the fava extract and the erythrocytes were used. Both saline and plasma were used as diluents. Similarly, no precipitin antigen-antibody response could be demonstrated by using serial dilutions of the fava extract and the patient's serum.

To circumvent the possible existence of tissue anergy, skin tests and passive transfer experiments were carried out approximately five months after recovery from the disease. Varying dilutions of the extract (from 1:100 to 1:1,000,000) were injected intradermally and readings were made in 15 minutes, 24 hours, and 36 hours. Buffered saline was used as a control. Thirty-four hours after the intradermal injection of a 1:100 dilution of the extract, a 12 mm. area of induration and erythema appeared and was gone in thirty minutes. All other skin tests were interpreted as negative. Passive transfer experiments in fifteen control patients also failed to show any skin reaction.

The failure to demonstrate an antibody response in our patient is not in keeping with the findings of the Italian investigators who believed that the hemolytic anemia of favism was an allergic phenomenon. Yet the interpretation of these results is difficult, for skin tests and passive transfer experiments may be negative in other well-known allergic states. Perhaps our patient was still in a refractory or anergic phase of tissue response when these tests were done.

SUMMARY

This report deals with the occurrence of an acute hemolytic anemia in an Italian child following the ingestion of two raw fava beans. Jaundice and anemia were the presenting symptoms. Convalescence was rapid and uneventful. No therapy except oral ferrous sulfate was given. The patient has remained in good health over a five-month period of observation.

Studies of the toxic properties of the fava bean and antibody response of the patient over five months failed to demonstrate definite sensitization as shown by skin tests, passive transfer experiments, and precipitin reactions.

The sudden onset of asymptomatic jaundice in an Italian child should necessitate careful questioning for a recent history of fava bean ingestion.

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HEMOPHILIA IN THE NEGRO

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INTRODUCTION

THERE exists in the minds of many physicians considerable doubt concerning the incidence of hemophilia in the Negro. Our recent observation, therefore, of a Negro family in which two boys presented the classic findings of hemophilia led us to a review of the subject and this report of our cases is an attempt to clarify our understanding of the occurrence of the disease among Negroes.

REVIEW OF THE LITERATURE

Standard textbooks of medicine and hematology[1] indicate that hemophilia occurs predominantly in Caucasians and only rarely in Negroes. More detailed review of the literature indicates that a number of cases (summarized in Table I) has been reported in Negroes, but critical evaluation of these reports throws doubts on the validity of the diagnosis in some instances. In order to evaluate these case reports properly it is well to reconsider the criteria essential to a diagnosis. Bulloch and Fildes,[2] in their exhaustive monograph on the subject summarized hemophilia as "an inherited tendency in males to bleed." This succinctly describes the clinical features of the disease which reflect the laboratory findings of a prolongation of the coagulation time of the blood, as first described by Wright[3] in 1891. Although subject to wide spontaneous fluctuation, sometimes even approaching upper limits of normal, this laboratory manifestation, once demonstrated, is practically diagnostic in the presence of a normal plasma fibrinogen level.

In addition to validity of diagnosis we were particularly interested in the racial background of those patients in whom authentic hemophilia occurred. Specifically, an attempt was made in each of these cases to determine from the data presented whether the patient was of pure Negro ancestry or of mixed racial origin.

Our studies indicate that at least eleven case reports of "hemophilia" in Negro patients has been published. The earliest report was that by Hadlock of Cincinnati in 1874.[4] This report indicated that the father of the patient died of hemophilic hemorrhage. Since hemophilia is not transmitted directly by the male, it is unlikely that this was an instance of true hemophilia. The bleeding in this case was most likely due to some other disturbance of hemostasis.

Koch's case[5] published in 1890 was of a female patient, and therefore probably was not a case of true hemophilia. For similar reasons Steiner's case[6] in 1900 probably should not be considered. In the same year Buck reported

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TABLE I

AUTHOR	CASE SUMMARY	COMMENT	RACIAL ORIGIN
Hadlock (1874)	History of uncontrollable breeding from tooth socket in a 7-year-old mulatto boy. Only one such episode was reported. The father of this patient bled to death as a result of a briar scratch; an uncle, of hemorrhage from a laceration inflicted by a scythe. No laboratory substantiation of diagnosis. Genetically not compatible with hemophilia.	Diagnosis questionable	Mixed
Koch (1890)	The patient was a 6-year-old Creole, a girl whose history of bleeding was limited to a single episode of hemorrhage from the oral cavity.	Not hemophilia	
Steiner (1900)	This was a 14-year-old girl. Her pedigree revealed evidence of bleeding in both the male and female members of the family. This was reported as "the second case of hemophilia in the Negro." Sex incidence is against the diagnosis of hemophilia.	Not hemophilia	
Buck (1900)	This was an extremely brief communication concerning two patients, one of which was female. Both subjects had experienced severe nosebleeds. The ethnologic factors were not discussed.	(a) Female patient not hemophilia (b) Insufficient evidence for diagnosis of hemophilia in the male patient	
Taylor (1923)	This patient, a man, had experienced frequent episodes of bleeding as a child. Several of the male members in his family had hemorrhagic tendencies. The clotting time was consistently prolonged. Author significantly commented that the patient was "apparently tinctured with white blood."	Compatible with diagnosis of hemophilia	Mixed
Crandall (1936)	This patient, a ten-year-old boy, had bled frequently and profusely following episodes of mild trauma. The family history traced back for several generations revealed no evidence of bleeding among the male or female members. The laboratory data were quite complete and were compatible with the diagnosis. Sporadic nature of case would make plasma fibrinogen level desirable for more definitive diagnosis. Crandall described patient as being "very dark." Similarly, his parents and the siblings were heavily pigmented Negroes.	Compatible with the diagnosis of sporadic hemophilia	Pure Negro
Pachman (1937)	Pachman reported three cases, all in boys. The 15-year-old patient had a prolonged bleeding time and the author seemed inclined to consider his bleeding to have an allergic background. The other two boys, 13 and 6 years old, had histories of frequent hemorrhage in early infancy. The pedigree suggested among the male patients a transmissible tendency to excessive bleeding. The laboratory data were entirely compatible with the diagnosis.	The older child was probably not a hemophiliac; the two younger boys were	One of mixed; one purely Negro
Birch (1937)	Three of the series of ninety-eight cases of hemophilia were Negroes of mixed racial origin.	Compatible with diagnosis of hemophilia	Mixed
Campbell (1939)	A 22-year-old man with clinical and laboratory features of hemophilia. The pedigree presented evidence of abnormal bleeding tendencies in male members of the family. Photograph of patient indicates mixed racial origin.	Compatible with diagnosis of hemophilia	Mixed

two cases,[7] one of which was of a female patient and therefore was eliminated by us as a true hemophilia. The information and data on the male patient were too meager to satisfy diagnostic requirements.

In 1923 Taylor[8] reported what was probably the first case of true hemophilia in a Negro. The genetic, clinical, and laboratory findings were presented in detail and substantiated the diagnosis. The author commented that the patient was of mixed racial ancestry.

Crandall, in 1936, presented a very significant case report.[9] His data satisfied all the essential diagnostic criteria. However, careful inquiry revealed no evidence of hemophilia in the patient's family. This does not preclude the diagnosis. Birch[10] has pointed out that a familial history is desirable but not absolutely essential to a diagnosis. These individuals with all except the genetic criteria of the disease are considered "sporadic" in contrast to the "hereditary" type. One other pertinent feature of Crandall's case is that the patient was apparently of a purely Negro origin. The description of the child's physical features as well as those of his family seemed to corroborate this. Crandall's case is, therefore, the first authentic report of hemophilia in a presumably pure Negro.

Pachman, in 1937, reported three cases of hemophilia in Negroes.[11] He pointed out, however, that in one case the bleeding was probably due to anaphylactoid purpura. In the other two cases the histories, symptoms, and laboratory findings were quite compatible with the diagnosis. One of these presented physical characteristics of racial intermixture whereas the history and physical characteristics of the other suggested a purely Negro racial origin with a typical hemophiliac geneology.

The most recent case published by Campbell[12] in 1939 had characteristics quite typical of hemophilia, but the author noted that the patient was definitely of mixed racial ancestry.

In addition to these case reports specifically concerned with hemophilia in Negro patients, other authors have mentioned the racial aspects of hemophilia in publications considering the subject generally. Birch[10] reported that three of her series of ninety-eight hemophiliacs were Negroes of mixed racial origin.

CASE REPORTS

CASE 1.—H. W., a two-year-old boy, was first admitted to the University of Illinois Hospitals in July, 1946, because of bleeding from the upper gingivae for the previous twenty-four hours. The patient was a known "bleeder" at the time of admission and had been bedridden for two weeks previously as a result of swollen joints. The past history indicated that the patient had always manifested a tendency to bleed readily. His joints swelled readily following mild trauma.

Birth history indicated that he was born by a full-term, spontaneous delivery. There was no obstetrical instrumentation; no hemorrhage was noted at birth.

The pedigree of the family is presented in Fig. 1. The patient's father was 37 years old and in good health. No information was obtainable concerning either of his parents. The patient's mother was 24 years of age and well. Her

mother died of tuberculosis. Her mother's sister had two children stated to be bleeders. One child died at the age of 5 as a result of "internal hemorrhages." The other child had seven crippling deformities due to repeated hemorrhages.

One male sibling, 3½ years of age, was also a known bleeder (Case 2). Two female siblings, one 4½ years and one 6 months of age, respectively, were living and well. No evidence of abnormal bleeding had been observed in them. A definite history of racial mixture five generations previously was obtained.

Physical examination revealed a young, cooperative, Negro boy aged 2 years, who was bleeding profusely from the frenum of the tongue. A slight mucoid nasal discharge was present. Several ecchymotic areas were present over the left forearm and elbow. The temperature was 99.6° F. rectally, the pulse 102, and the respirations 24 per minute. The skin was light brown; facial features were somewhat Caucasian.

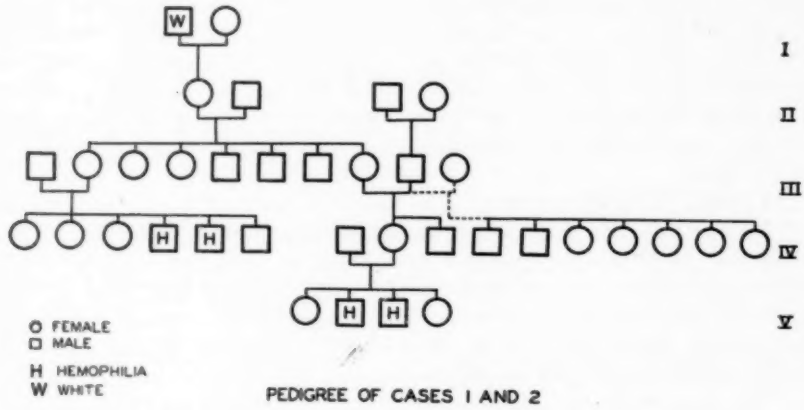

Fig. 1.

Laboratory examination revealed the following: Urinalysis was normal; red blood cell count, 4.75 million per cubic millimeter; white blood count, 14,000 per cubic millimeter; differential blood smear, 55 per cent lymphocytes, 41 per cent neutrophiles, 2 per cent monocytes, 2 per cent eosinophiles. No abnormal cells were observed. Platelets were within normal limits; clotting was completed in 120 minutes (Howell's method); clot retraction was complete in six hours; the plasma fibrinogen level recorded on a later admission was 0.357 mg. per 100 c.c. of blood (normal 0.3 to 0.6 mg).

The family history, clinical history, physical and laboratory findings, all supported the diagnosis of hemophilia.

The patient was given 250 c.c. of citrated whole blood intravenously. Twenty-four hours later all signs of bleeding had disappeared and patient was discharged in good condition.

CASE 2.—This patient, W. W., a 4-year-old Negro boy (brother of Case 1) was admitted to the University of Illinois Hospitals in June, 1947, because of painful and swollen joints for the previous twelve hours.

The history revealed that at 9 months of age the child experienced a severe hemorrhage about the left shoulder. Since that episode he was observed to bleed readily and for prolonged periods. He was a full-term infant; the delivery was spontaneous and normal. No evidence of hemorrhage was noted at birth.

Developmentally he was normal. The family history was the same as that given for Case 1 and is summarized in Fig. 1.

Physical examination revealed a thin but well-developed Negro child. He lay quietly but objected to movements of the right arm. He was cooperative, quiet, and polite. He had several ecchymotic areas 2 to 4 cm. in diameter over the left supraspinous region of the thorax. The right elbow and right knee were warm, swollen, and tender. The skin was dark brown; some Caucasian facial features were noted.

Laboratory findings were as follows: red blood count, 3.7 million per cubic millimeter; white blood count, 11,000 per cubic millimeter; differential blood smear, 57 per cent neutrophiles, 4 per cent stab forms, 35 per cent lymphocytes, 4 per cent monocytes. Coagulation time, 130 minutes (Howell's method); clot retraction was complete in seven hours; bleeding time was within normal limits; urinalysis was normal.

Because of the family history, clinical history, physical and laboratory findings, a diagnosis of hemophilia was made.

The patient was given small doses of barbiturates and analgesics for his discomfort. The joint swellings subsided somewhat and he was discharged in good condition after four days of hospitalization.

Progress Reports of Cases.—Since their initial admissions these patients have been hospitalized repeatedly for episodes of moderate and severe hemorrhage. Most of these have followed trauma. In general, their hemorrhagic manifestations have responded well on each occasion to bed rest, small blood transfusions, and more recently to intramuscular injections of 10 mg. antihemophilic globulin of Fraction 1 (Cohn), which has produced prompt clinical cessation of hemorrhage plus demonstrable reduction in coagulation time for eighteen to twenty-four hours following the injection. Now at the ages of 4 and 5 years, respectively, they are robust children except for their frequent incapacities resulting from hemorrhage.

COMMENT

A review of the literature and this report of our cases support the impression that hemophilia does occur in American Negroes. Detailed analysis of these cases indicates that most of these individuals are of mixed racial origin on examination of their pedigrees and physical characteristics. In our two cases the pedigree presented definite evidence of Caucasian intermixture in previous generations; the patients physically evidenced this mixed racial background.

The question concerning the occurrence of hemophilia in racially pure Negro individuals cannot be entirely answered at present. Of the reported cases, that recorded by Crandall[9] was the first one in which the pedigree information (though limited) and anthropological features are compatible with a purely Negro racial origin. The diagnosis was well established although a plasma fibrinogen level to exclude the rare possibility of congenital afibrinogenemia would have been more conclusive. Since no known hemophiliacs were present in the background of this patient, it must be regarded as a case of sporadic hemophilia.

Although Bulloch and Fildes minimized the incidence of sporadic hemophilia with the statement "these 'de novo' bleeders were few in number and would be still fewer if the authors had sufficient time to investigate beneath

the surface,'' they did concede that such cases do occur. The British biologist Haldane,[13, 14] however, emphasizes the role of sporadic cases of hemophilia arising as a result of mutation of sex-linked genes as playing a very significant role in the perpetuation of this disease.

Of the cases reported by Pachman[11] two presented the classical features and geneology of hemophilia. The history and physical features of one suggested a purely Negro origin. This is the only reported case satisfying all the criteria for the diagnosis of hemophilia in a presumably pure Negro. It should be noted, however, that the racial background of many Negroes is not accurately known.

For a definitive answer concerning the occurrence of hemophilia in racially pure Negroes, a study of a large population would be necessary. Because of the practical difficulties involved in undertaking such a study, authorities who had devoted much time to the study of both the West African and American Negro populations were consulted.[15, 16] Their studies revealed no evidenc of the existence of this disease either from the folklore of the people or by actual observations of large numbers of individuals. Since they were not specifically interested in this problem at the time of their studies, these observations cannot be interpreted as conclusive. It is obvious that the comparison of large population groups of racially pure and racially mixed individuals would do much to elucidate the true racial incidence of not only hemophilia but many other diseases believed to be influenced by race. It is hoped that further observations by physicians concerning the racial incidence of hemophilia will be reported.

SUMMARY

The occurrence of hemophilia in the American Negro has been reviewed briefly and two cases of mixed racial origin have been reported. While hemophilia with characteristic genetic background occurs in American Negroes of mixed racial origin, the disease has been noted only once sporadically and once with characteristic genetic background in individuals of presumably pure Negro ancestry. Although hemophilia has not been noted in the West African Negro and racially pure American Negro by students of these populations, further studies of these groups would be indicated to establish this fact more definitely.

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ACRODYNIA: A SUMMARY OF BAL THERAPY REPORTS AND A CASE REPORT OF CALOMEL DISEASE

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BILDERBACK'S classical description of acrodynia[1] emphasizes the fact that there has been no known etiology and therefore no specific therapy for the disease. Much interest has arisen in the new approach to the disease contained in our report in the JOURNAL OF PEDIATRICS,[2] based on the suggestion by Warkany and Hubbard,[6] of mercury as an etiologic agent and the clinical use of BAL in therapy.

Thanks to the cooperation of pediatric colleagues it has been possible to accumulate further data which seem worthy of publication at this time.

Watkins,[3] states that Zahorsky[4] was on the brink of the discovery that mercury was an etiologic agent in acrodynia but turned away from the theory when he could obtain no history of calomel intake in all his cases.

Davidson[5] tells me that Dr. Lesesne Smith, Sr., suggested to him between 1934 and 1938 that mercury was involved in the cause of acrodynia.

Warkany and Hubbard[6] finally produced the laboratory proof of the presence of mercury in the urines of acrodynia patients and they have lately published a report[7] of the findings in twenty cases of acrodynia. In communication with Dr. Warkany it was found that there was an overlapping of their figures with some of my reports so that in the tables I am giving their figures as fifteen instead of twenty.

Fanconi Botsztejn and Schenker[8] have recently published the report of a disease resembling acrodynia which they call calomel disease. It is chiefly characterized by a macular rash resembling in appearance that of red measles and caused by the ingestion of mercury in the treatment of intestinal parasites. I am adding the report of such a case to this paper.

Table I gives a summary of the cases of clinical acrodynia which have appeared in the literature or have come to my attention through personal communications.

TABLE I. URINE REPORTS IN CLINICAL ACRODYNIA

AUTHORS	WITH PROVED MERCURY	NO MERCURY FOUND	NO URINALYSIS
Warkany and Hubbard[7]	13	2	—
Elmore[9]	2	—	—
Costner[10]	2	—	1 (teething powders)
Smith, L.[11]	1	—	—
Bivings and Lewis[2]	1	—	—
Fox (London)[12]	2	—	8 (teething powders)
Ravenel[13]	2	—	—
Gipson[14]	—	—	2 (1 teething powders)
Christie[15]	—	1 (teething powders)	—
Watkins, Ashe and Moore[3]	2	—	—
Cook[16]	—	—	1 (teething powders)
Lewis (Eggleston Hospital)[17]	3	—	1 (teething powders)
Totals	28	3	13

Grand total forty-four cases of clinical acrodynia.

Comment on Table I.—Of thirty-one patients with clinical acrodynia on whom mercury determinations were done, twenty-eight showed mercury. Warkany[5] states that he and his associates observed three children whose urines showed the presence of mercury in appreciable amounts following ingestion of mercury and who showed no signs of clinical acrodynia.

There were three patients in whom mercury could not be found.

Of thirteen patients on whom no mercury determinations were done, twelve had histories of the use of teething powders. (Those commonly used contain from $\frac{1}{10}$ to $\frac{1}{8}$ grain of calomel.)

Table II shows the reports of the results of BAL therapy as reported in fifteen patients seen by several different observers.

TABLE II. BAL THERAPY IN CLINICAL ACRODYNIA

AUTHORS	PROMPT IMPROVEMENT OR RECOVERY	SLOW IMPROVEMENT
Bivings and Lewis[2]	1	—
Fox[12]	1	1
Elmore[9]	2	—
Smith[11]	1	—
Costner[10]	1	1
Gipson[14]	—	2
Christie[15]	1	—
Cook[16]	1	—
Watkins, Ashe, and Moore[3]	3	—
Totals	11	4

Comments on Table II.—These reports came from widely separated observers and some lacked important details necessary for accurate analysis. The disease is known to vary widely in its clinical course and most patients recover spontaneously but usually only after a prolonged illness. It was the opinion of most of the observers in this series that BAL therapy seemed to be of definite benefit.

Acrodynia does not appear with sufficient frequency in this area to permit one observer to accumulate a large series short of many years' time. Since it was possible for Fox[12] to find ten cases in a brief period of time it would seem to be of much greater frequency in England and it is said by Bilderback[1] to occur quite frequently in Australia. It is hoped that larger series will be reported where controls can be run and a single observer or group of observers can check the results of BAL therapy.

The dosage outlined in my original report was followed in this series. In view of the reports of Woody and Kotemani[18] it is probable that the dosage could be increased safely to at least 5 mg. per kilogram for the first day in severe cases and in extremely severe cases an even higher dose might be given with due allowances for the toxicity of the drug.*

In this group teething powders were the source of mercury in a large majority of cases, calomel in a few, ammoniated mercury ointment in one, and mercury bichloride diaper rinse in one case. Since ammoniated mercury is commonly used on the newborn infant, sensitization easily might occur quite early in life.

*Dr. Fox writes me that Owen of the Imperial College of Science, working with Danielli and collaborators, has made a BAL-glucoside which is much more water soluble and much less toxic than BAL. Unfortunately the chemisty is difficult, they have not been able to put the material into ampules, and, therefore, there have been no clinical trials as yet.

SUMMARY AND CONCLUSIONS

Evidence is offered which would seem to indicate that mercury has some part in the etiology of acrodynia. If this assumption is correct it would seem that BAL therapy is logical. The cases herewith reported on whom it was used would seem to indicate it has some value.

CALOMEL POISONING, A CASE REPORT

Baby J. B., aged 9 months, weighing 18 pounds, was brought to my office June 24, 1948, because of a rash for four days.

There were no physical findings of importance other than the rash and there was no fever. The baby was extremely restless and irritable. The rash was macular in type and covered the entire body, scalp, extremities, and the palms of the hands and the soles of the feet. The toes and the fingers were pink at the distal ends. The general appearance of the rash was that of a well-established red measles but there was no cough, no fever, no Kopliks spots, no conjunctivitis or photophobia.

The mother stated that she had used teething powders for rubbing the gums for two or three successive days one week previously and since there was some resemblance to the symptom complex of acrodynia a urine specimen was requested.

The urine specimen was examined by Warkany and Hubbard on June 27 and they reported to me several days later that mercury was present in a concentration of 50 gamma per liter.

On June 25 the rash was fading and on June 27 had faded completely. Total duration was seven days, with no therapy.

In discussing the case with Dr. Warkany he suggested it more nearly resembled calomel poisoning recently described by Fanconi and collaborators[8] than true acrodynia. Study of Dr. Fanconi's paper, especially the natural color photographs, confirmed this belief.

Recovery was spontaneous and the disease was of short duration.

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PNEUMOMEDIASTINUM IN THE NEWBORN INFANT

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CYANOSIS in the neonatal period presents a difficult problem in differential diagnosis; that pneumomediastinum is one of the important possible causes is illustrated by the case recorded herewith. A few reports of this syndrome have appeared in the literature but they seem to have attracted little notice in the evaluation of neonatal mortality.

In 1940 when Gumbiner and Cutler[1] reviewed the literature, they could find only eight cases of pneumomediastinum in infants, of which the first two, discovered at autopsy, were reported by Guillot[2] in 1853. Two cases were reported by Schuler,[3] and one each by Kirchgessner,[4] H. K. Farber,[5] Rosenblum,[6] and Poeck.[7] Gumbiner and Cutler[1] stressed the importance of pneumomediastinum as a cause of death in the newborn infant as well as the diagnostic value of lateral roentgenograms of the chest. They were the first to report the therapeutic use of needle aspiration. Since 1940 twelve additional cases have been reported (see Table I), including three by Lowman and Culotta,[12] of which one showed the classical clinical syndrome of circulatory and respiratory embarrassment with precordial bulge. (This infant died before needle aspiration could be attempted.)

CASE REPORT

K. D., a one-day-old male infant, was extremely cyanotic, comatose, and scarcely breathing when admitted to Abington Memorial Hospital. Delivery had been spontaneous without instruments at another hospital. Respiration was slower than usual in becoming established but resuscitation had not been necessary, and nothing abnormal had been noted by the attending physician on examination of the infant after delivery. Twelve hours later cyanosis was first observed. The cyanosis deepened progressively and the infant was referred to the Abington Hospital twenty-four hours after birth.

On arrival he was comatose and appeared moribund. The skin was "purplish-black" in color, with numerous petechiae scattered over the thorax and abdomen. The anterior fontanel was not bulging. Slight, symmetrical respiratory excursions and an early precordial bulge were noted. Fine, diffuse râles were heard over the right lung. These were more marked at the base. Breath sounds over the left lung were moderately diminished. The heart could not be outlined by percussion. Heart sounds were best heard in the midsternal region but even there were almost inaudible. No murmurs were heard.

Oxygen by mask was administered immediately, and caffeine sodium benzoate, 60 mg., was given intramuscularly. Within one hour the rate and depth of respiration had improved, and a decrease in cyanosis was noted. Oxygen therapy was continued, and during the following twelve hours the cyanosis diminished and the infant's general condition improved. The respiratory rate, however, still approximated 80 per minute. There was noted at this

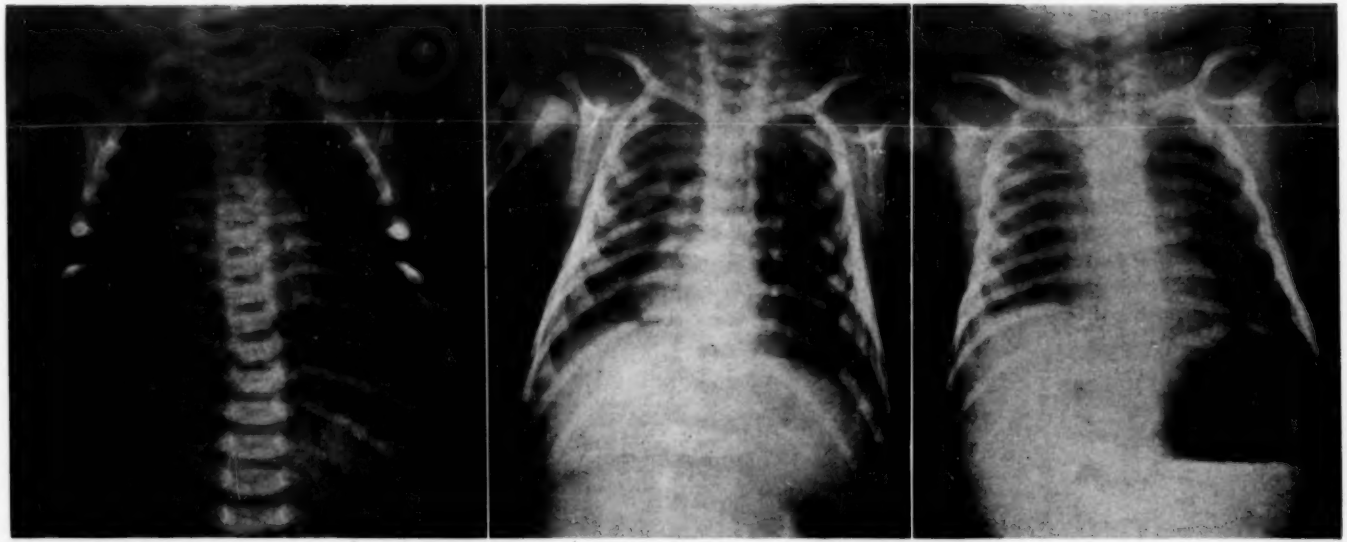

Fig. 1. Fig. 2. Fig. 3

Fig. 1.—Anteroposterior view, thirty-six hours after birth and prior to needle aspiration. Atelectasis of the right upper lobe. (Bedside x-ray taken while child was in critical condition.)

Fig. 2.—Anteroposterior view sixty-four hours after birth sixteen hours after 17 c.c. of air were aspirated. Atelectasis is no longer present.

Fig. 3.—Seven days after birth. Normal chest film prior to discharge from hospital.

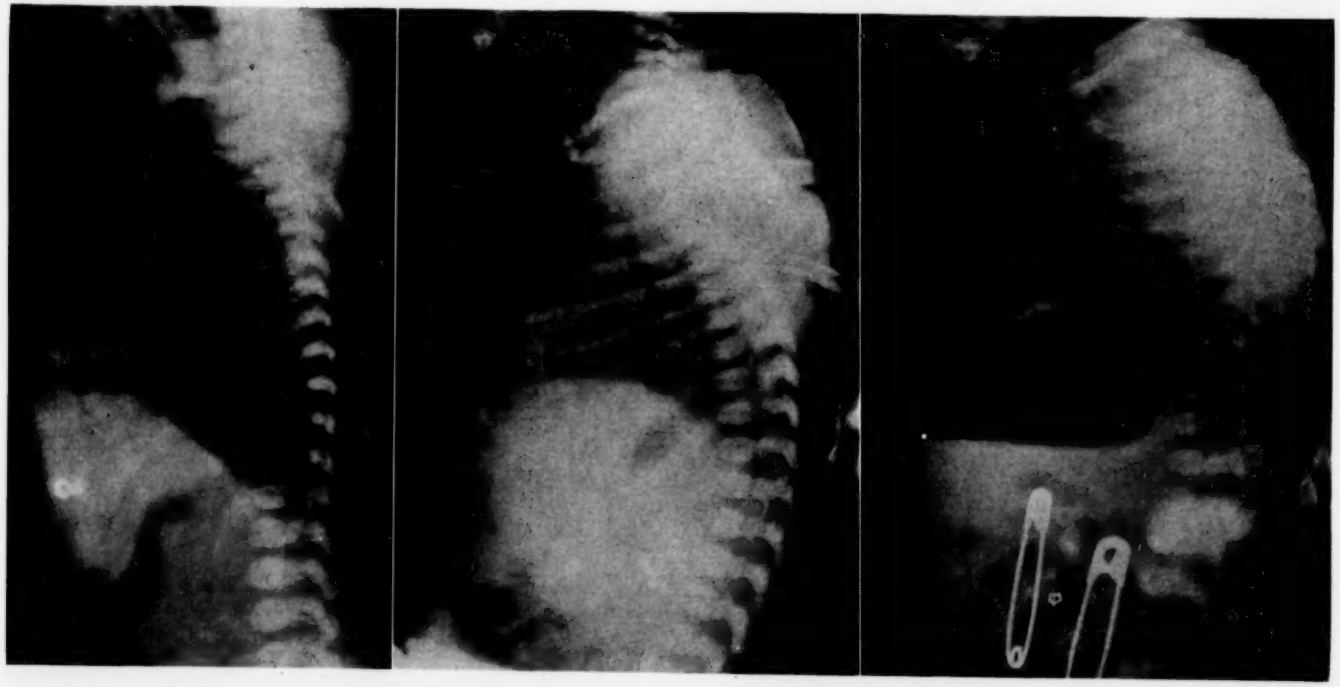

Fig. 4. Fig. 5. Fig. 6.

Fig. 4.—Lateral view, thirty-six hours after birth and prior to needle aspiration. Air is seen in the anterior mediastinal space. The heart is displaced posteriorly.

Fig. 5.—Lateral view, sixty-four hours after birth, and sixteen hours af ter 17 c.c. air were aspirated. Less air is seen in the anterior mediastinal space, than in Fig. 4.

Fig. 6.—Lateral view, seven days after birth. Normal chest film preceding discharge from the hospital.

TABLE I

AUTHOR	CASE	YEAR	AGE OF PATIENT	CYANOSIS	DYSPNEA	ATELECTASIS	ML. AIR OBTAINED*	RESULT
Gumbiner and Cutler[1]	Case 1	1940	30 hr.	Extreme	Severe	Patchy	6	Rec.
	Case 2			Slight	Slight			Rec.
	Case 3			Slight	Slight			Rec.
	Case 4			Moderate	Moderate			Rec.
De Costa[8]†		1940	12 hr.‡	Present				Rec.
Fisher[9]		1941	12 hr.‡	Extreme	Severe	L. Lung		Death‖
Biering[10]		1941	12 hr.‡	Moderate	Moderate	R.U.L.	No	Rec.
Smith and Bowser[11]	Case 1	1942	12 hr.‡	Extreme	Severe		Yes§	Rec.
	Case 2		12 hr.‡	Severe		R. Lung	No	Rec.
Lowman and Culotta[12]	Case 1	1945	12 hr.‡	Extreme	Severe		No	Death
	Case 2		12 hr.‡	Slight	Slight		No	Rec.
	Case 3		12 hr.‡	Moderate	Moderate		No	Rec.
Heald and Wilder	Case 1	1948	12 hr.	Extreme	Severe	R.u.L.	17	Rec.

*By therapeutic needle aspiration of mediastinum (parasternal).
†A Second case mentioned, but not described. Aspiration, 6 c.c. air, site not specified.
‡First symptoms noted about twelve hours following birth.
§Air, under pressure, aspirated, but amount not specified.
‖Pulmonic interstitial emphysema found at autopsy.

time a marked precordial bulge with the physical findings of emphysema over the entire thoracic cage.

A roentgenogram of the chest showed collapse of the right upper lobe, and widening of the mediastinum bilaterally. The lateral view showed air confined to the anterior mediastinal space, with posterior displacement of the heart.

About forty-eight hours after birth the infant's condition became critical. The respiratory rate was 88 and the sternal region bulged anteriorly in a striking manner. A 20-gauge needle was inserted into the third interspace just to the right of the sternum and 5 c.c. of air were aspirated without difficulty. Following this procedure there was definite but slight improvement. A second aspiration performed three hours later yielded 12 c.c. of air, and this was followed by great improvement during the next twelve hours.

Because of the marked degree of hyperventilation that was present during the critical stages of the illness, blood chemical determinations were obtained. Bicarbonate was 10.5 meq. per liter and the chlorides 107.5 meq. per liter. This acidosis was corrected by the administration of 150 c.c. of 1/6 molar sodium lactate by hypodermoclysis.

During the twenty-four hours following needle aspiration the temperature ranged between 99.6 and 103° F. Ten thousand units of penicillin were given intramuscularly every three hours. On the third day of treatment the temperature was normal and remained so until discharge from the hospital. The precordial bulge subsided within thirty-six hours following the needle aspirations. The respiratory rate fell gradually so that on the tenth hospital day it was 30 per minute.

COMMENT

In 1939 Macklin[13] first described the results of his studies on the pathogenesis of pneumomediastinum in experimental animals. He stated that the pathologic process begins whenever the anatomy of the lung is so altered that a localized or generalized emphysema is the end result. Such emphysema gives rise to overdistention of the alveoli with air finding its way into the pulmonary vascular sheaths. The actual inlets for the air into the sheath system are multiple, minute ruptures in the alveolar bases which overlie the finer ramifications of the pulmonary blood vessels. The air then dissects down the sheaths to the hilum of the lung and from there into the mediastinum. In none of his experimental animals was Macklin able to demonstrate torn or ruptured alveoli grossly. This process, as described above, is known as pulmonic interstitial emphysema.

Further extension of this process, with the air invading the mediastinum, gives rise to pneumomediastinum. The pressure in the mediastinum may become so great that either death ensues or decompression occurs by extension of the process in one of three directions: (1) down into the retroperitoneal space and even further into the groin and leg; (2) upward into the axilla, the wall of the chest, the root of the neck, and the face; (3) forward between the parietal pleura and the pericardium to appear as large blebs overlying the heart.

It is the third type of extension which gives rise to the distressing symptoms described in the case reported. The negative pressure in the anterior mediastinum becomes positive with resultant pressure on the large veins to the heart. This results in diminished venous return and circulatory embarrassment. The pressure in the anterior mediastinum can be relieved in one of two

ways: (a) by needle aspiration and (b) by rupture of the mediastinal wall into the pleural space with resultant pneumothorax. Experimentally, Macklin[13] has shown that the mediastinal wall, strained past endurance, ruptures into the pleural space, causing pneumothorax. This relieves mediastinal pressure, thus improving the circulation; and, at the same time, by collapsing the lung and eliminating the area of alveolar distention, it prevents further leakage.

According to the above reasoning, the development of spontaneous pneumothorax should be regarded as a fortunate mechanism whereby pneumomediastinum is relieved. Our case and the others represent a syndrome which results from a failure of this mechanism to operate in the face of a marked mediastinal emphysema. Although these severe cases are relatively rare, it is probable that pneumomediastinum as a precursor of pneumothorax has about the same incidence as the latter, which, in the newborn infant, is said to be 1 per cent.[14]

SUMMARY

Pneumomediastinum in a newborn infant can produce an alarming and unusual clinical picture characterized by: (1) extreme cyanosis; (2) marked precordial bulge; (3) almost absent heart sounds; (4) rapid shallow respirations.

Anteroposterior and lateral films of the chest in the case described showed atelectasis of the right upper lobe and air in the anterior mediastinum. The lateral film is pathognomonic of this syndrome. Relief of symptoms (essentially cardiac) was obtained by needle aspiration of the anterior mediastinum, from which 17 c.c. of air was obtained. Recovery was uneventful.

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THE OCCURRENCE OF A TYPE FIVE SULFADIAZINE-RESISTANT HEMOLYTIC STREPTOCOCCUS

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INTRODUCTION

THE circumstances and conditions which led to the development of sulfonamide-resistant hemolytic streptococci have been reviewed recently.[1] Available information suggests that conditions of continuous mass sulfadiazine prophylaxis as they existed in the Armed Forces during World War II[2, 3] were conducive to dissemination, and possibly to the development of strains of hemolytic streptococci resistant to the action of sulfadiazine.

The spread of sulfonamide-resistant hemolytic streptococci to the civilian population has received little attention. The first reported instance of civilian infections due to these resistant organisms occurred in 1946 when Johnson and Hartman[4] described a small epidemic due to a sulfadiazine-resistant group A, type 19 hemolytic streptococcus, in Cooperstown, N. Y. Another survey made in Boston[1] revealed one infection due to a group A, type 19 sulfadiazine-resistant hemolytic streptococcus out of 167 infections studied. In both instances it was concluded that the resistant organisms encountered in these civilian populations were of the same type as occurred in the Armed Forces and had probably been introduced by Army or Navy personnel. The possibility of sulfonamide-resistant strains of hemolytic streptococci developing in the general population has received little investigation, and no reports of such an occurrence have appeared in the literature to date.

Because sulfadiazine-resistant, group A, hemolytic streptococci had been encountered in Cooperstown in 1946,[4] it was decided to test the sulfonamide sensitivity of hemolytic streptococci in this community eighteen months later to determine if these resistant type 19 organisms had persisted and were still a cause of infections. It is the purpose of the present communication to report the results of this survey in which a moderately sulfadiazine-resistant group A, type 5 hemolytic streptococcus was encountered, and also to comment on some of the factors pertinent to its occurrence.

MATERIALS AND METHODS

The sources of hemolytic streptococci were cultures from both adults and children from Cooperstown and surrounding areas who were seen in the outpatient department or wards of the Mary Imogene Bassett Hospital from January to May, 1948. These patients had clinical evidence of a streptococcal infection or were admitted to the hospital for observation or study and were

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found to harbor hemolytic streptococci. Most of the strains of hemolytic streptococci were obtained from the nasopharynx of patients who had pharyngitis, but others were isolated from infected wounds, abscesses, draining ears, vaginal discharges, and blood cultures. No attempt was made to do a widespread survey on a healthy group to determine carrier rates.

Culture swabs were streaked on the surface of 5 per cent rabbit blood agar plates which were incubated for twenty-four hours at 37° C. Single colonies of beta-hemolytic streptococci were transferred to broth on the following day and following incubation were checked for purity by restreaking on blood agar.

All hemolytic streptococci isolated were grouped and typed by the capillary precipitin technique[5] with the available diagnostic sera. Due to the difficulty of obtaining typing sera for all types, sera only for those types some strains of which were known to be sulfonamide-resistant were used, i.e., types 1, 3, 6, 17, and 19. Upon encountering type 5 resistant strains, all cultures were typed using this serum also. The sulfonamide sensitivity was determined by the method of Wilson,[6] using horse serum and sodium sulfadiazine; known resistant and sensitive strains were always run as controls.

RESULTS

Ninety-six strains of group A hemolytic streptococci isolated from patients in Cooperstown and its environs were tested for sensitivity to the action of sulfadiazine. The type distribution determined by the use of the six available diagnostic sera and sulfonamide sensitivity are listed in Table I.

TABLE I. TYPE* DISTRIBUTION AND SULFADIAZINE RESISTANCE OF GROUP A HEMOLYTIC STREPTOCOCCI

INFECTING TYPE	NO. CASES	NO. SULFADIAZINE-RESISTANT STRAINS
1	8	0
3	0	0
5	6	2†
6	1	0
17	0	0
19	0	0
NC‡	81	0
Total	96	2

*Only six sera (types 1, 3, 5, 6, 17, and 19) were available for typing by the precipitin method.

†These two type 5 strains were resistant to 5 mg. per cent sodium sulfadiazine.

‡NC indicates strains not classified by the precipitin method with available diagnostic sera.

Six type 5 hemolytic streptococci were encountered in this study, of which two strains showed evidence of moderate resistance to the action of sulfadiazine, i.e., grew in 5 mg. per cent sodium sulfadiazine. These type 5 strains were isolated from children 11 years of age or younger (see Table II). All of the other strains were completely susceptible in vitro to sulfonamide action. No type 19 sulfonamide-resistant strains, which had been present in this locality previously,[4] were isolated.

Since this is the first report of the isolation of sulfadiazine-resistant group A, type 5 hemolytic streptococci in the general population, further analysis of

TABLE II. CLINICAL DATA OF TYPE FIVE INFECTIONS

PATIENT	AGE	DIAGNOSIS	DATE OF CULTURE	TREATMENT PRIOR TO CULTURE	SULFADIAZINE RESISTANCE	REMARKS
M54	11	Tonsillitis and pharyngitis	3/ 5/48	Received a combination of sulfadiazine and sulfathiazole 6 days prior to culture.	1 mg.	Two weeks later patient developed nephritis and active rheumatic heart disease.
M66	5	Acute tonsillitis	3/17/48	None prior to culture.	1 mg.	Responded to treatment with sulfadiazine.
M82	8	Pharyngitis	3/29/48	None prior to culture.	1 mg.	Responded to treatment with sulfadiazine and sulfathiazole.
M86	8	Pharyngitis	3/30/48	None prior to culture.	1 mg.	None.
M94	9	Pharyngitis	4/ 3/48	None prior to culture.	5 mg.	Responded to treatment with sulfadiazine.
M95	10	Pharyngitis	4/ 5/48	None prior to culture.	5 mg.	Responded to treatment with sulfadiazine.

the clinical data pertinent to this occurrence has been attempted (see Table II). The first patient (M54) from whom a type 5 strain was isolated had received a combination of sulfadiazine and sulfathiazole for six days prior to the time of his culture; the organism isolated from his throat grew in 1 mg. per cent sodium sulfadiazine; two weeks later this patient developed nephritis and active rheumatic heart disease. The next three type 5 isolations also grew in one milligram per cent sodium sulfadiazine; none of these patients had a history of sulfonamide treatment prior to culture. Of these patients two were treated with sulfadiazine or a combination of sulfadiazine and sulfathiazole and recovered promptly from their infections without complications; one received no treatment.

The patients (M94 and M95) who were infected with the type 5 hemolytic streptococci resistant to 5 mg. per cent sodium sulfadiazine were diagnosed as having a pharyngitis, were treated with therapeutic doses of sulfadiazine and made an uneventful recovery. These patients had not been given any sulfonamide medication prior to the time that they were cultured.

The patients with type 5 infections lived in different localities in the community and gave no history of any contact or association with one another. The two resistant type 5 organisms and also the nonresistant type 5 strains were sensitive to 0.015 units of penicillin as determined by the method of Rammelkamp.[7]

During this period of study the type 5 infections differed in no way clinically from those due to other types of hemolytic streptococci nor did they present any therapeutic or epidemiologic problem. The number of hemolytic streptococcal infections in this community during this period of study was considered to be average when compared with a similar period for other years. Sulfonamides are prescribed quite extensively in this area in usual therapeutic dosages for treatment of common infections, but chemoprophylaxis is employed rarely if at all.

DISCUSSION

The present report was initiated by a desire to determine whether sulfonamide-resistant type 19 hemolytic streptococci, which had been the causative organisms of a small epidemic in Cooperstown, N. Y., in 1946,[4] were still causing infections in this community after a lapse of eighteen months. The results of this study indicate that no type 19 organisms were encountered in ninety-six sporadic infections in 1948. Similarly, type 3 hemolytic streptococci, which were responsible for a large number of infections during the 1946 study,[4] were not encountered. Although mass carrier surveys of the general population were not carried out, the present data suggest that the population of this community was immune to type 19 and type 3 infections and that organisms of these types, if present, did not cause infections.

The isolation of two type 5 sulfonamide-resistant hemolytic streptococcus strains was unexpected. Neither the type 5 resistant strains nor the four nonresistant type 5 strains encountered were in any way unusual as far as the

type of infection they produced. Apparently the infections produced by these streptococci responded to sulfonamide therapy and in only one instance did any serious complications occur (see Table II).

The degree of in vitro sulfonamide resistance shown by the type 5 strains is not high, but is regarded as significantly elevated. By the Wilson method[6] sulfonamide-susceptible streptococci grow in the presence of zero and one milligram per cent sodium sulfadiazine but are inhibited by higher concentrations. Strains which are sulfonamide-resistant grow in the presence of 5, 25, or 125 mg. per cent of the drug. Epidemics due to type 3 hemolytic streptococci resistant to 5 mg. per cent sodium sulfadiazine were encountered during World War II.[8, 9] Few strains belonging to type 3 achieved resistance greater than this degree. The failure of chemoprophylaxis to offset epidemics due to these sulfonamide-resistant type 3 strains[8] suggests that resistance to 5 mg. per cent sodium sulfadiazine is of epidemiologic significance and may be of clinical significance.

The most common sulfonamide-resistant strains of group A hemolytic streptococci encountered in the Armed Forces during World War II were types 1, 3, 6, 17, and 19.[1, 9, 10] These type strains had degrees of sulfonamide resistance ranging from 5 to 125 mg. per cent sodium sulfadiazine. Although there are no reports of the occurrence of type 5 sulfonamide-resistant hemolytic streptococcal infections in the literature, type 5 organisms capable of growing in 1 mg. and 5 mg. per cent sodium sulfadiazine were encountered sporadically in the Navy,[9] but apparently did not present any epidemiologic or clinical problems.

As concerns the origin of the type 5 sulfonamide-resistant hemolytic streptococci encountered in this study, the most likely explanation is that they were the same as those encountered in the Navy during the mass chemoprophylaxis programs. The possibility that they could have arisen in the general population cannot be ruled out, but is not likely. Information referable to the possibility of sulfonamide-resistant hemolytic streptococci occurring in the general population is as follows: (a) all strains of hemolytic streptococci preserved prior to the advent of sulfonamide therapy which were tested for sulfonamide resistance were found to be sensitive to the action of sulfadiazine[1, 9]; (b) except for the type 19 sulfadiazine-resistant hemolytic streptococci, all other types encountered in the earlier study from Cooperstown[4] were sensitive to the action of sulfadiazine; (c) of more than 350 strains of hemolytic streptococci from Boston tested for sensitivity to sulfadiazine, only one resistant strain was isolated.[1, 11] All other surveys of the incidence of hemolytic streptococci having properties of increased resistance have been conducted in the Armed Forces and are not contributory to this problem in the general population. Although the civilian studies have not been extensive, they indicate that the occurrence of even moderately resistant strains of hemolytic streptococci has not been commonly encountered in strains isolated at random from civilian populations in two localities.

Whether or not hemolytic streptococci can develop resistance to sulfonamides in the civilian population during commonly prescribed dosages of sulfonamides is not definitely known. However, present data would seem to indicate that the treatment of patients with therapeutic doses of sulfonamides did not tend to cause the development of resistant strains of hemolytic streptococci.[12] Similarly, small groups of carriers of hemolytic streptococci did not develop resistant organism during varied regimens of chemoprophylaxis.[13, 14]

Experimental evidence concerning the mechanisms involved in the development of sulfonamide-resistant strains of hemolytic streptococci have not been reported to date. Preliminary observations[15] indicate that certain features of the sulfonamide resistance developed by hemolytic streptococci are similar to those of the resistance to penicillin by staphylococci and streptococci.[16, 17] Strains of hemolytic streptococci made resistant to sulfonamides by transfer in media containing increasing amounts of a sulfonamide develop resistance to the drug, only to lose this resistance when transferred in drug-free media. On the contrary, sulfonamide-resistant hemolytic streptococci recovered form human infections in the field have maintained their resistance after over 100 passages through media containing no drug. These observations would seem to indicate that in vitro resistance is of a temporary nature while in vivo resistance is permanent.

At present there is a paucity of information concerning the possibility of hemolytic streptococci acquiring resistance to sulfonamides, penicillin, or other antibiotic agents in the general population. Only when these organisms present epidemiologic or therapeutic problems do they receive any attention. The fact that a previously unreported sulfonamide-resistant type 5 hemolytic streptococcus has been observed in a civilian community indicates that the incidence of sulfonamide-resistant hemolytic streptococci in the general population, derived from the Armed Forces, may be greater than is generally realized. It is also of some interest that the two type 5 sulfonamide-resistant infections mentioned in this report occurred in children, since only one previous publication[4] has reported the isolation of sulfonamide-resistant hemolytic streptococci from children.

The possibility that hemolytic streptococci might develop resistance to sulfonamides in a civilian population could be determined only by extensive sampling under circumstances similar to those of this study. It is hoped that future surveys and fundamental investigation may elucidate the mechanisms concerned in this problem of sulfonamide-resistant hemolytic streptococci.

SUMMARY

The results of testing ninety-six strains of group A hemolytic streptococci for sensitivity to the action of sulfadiazine are reported. Two strains of type 5 hemolytic streptococci which were resistant to 5 mg. per cent sodium sulfadiazine are reported. The circumstances of the appearance of these resistant strains, in a civilian community, are discussed.

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THE ETIOLOGY OF ERYTHEMA NODOSUM

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WHILE erythema nodosum has long been recognized as a clinical entity most of the prevailing ideas concerning its etiology have developed within the past thirty years. At various times specific causative organisms have been advanced as the etiologic factor. Rosenau[1] isolated a polymorphous diplobacillus which he thought was the causative agent, but there has been no confirmatory evidence of it nor has any other organism been shown to be consistently associated with the disease.

For many years following the work of Mackenzie[2] a majority of workers have felt that erythema nodosum is closely related to the rheumatic syndome. Another group headed by Wallgren[3] and other Scandinavian workers has felt that tuberculosis plays an overwhelmingly important role in the etiology.

In more recent years erythema nodosum has been reported associated with coccidioidomycosis,[4] lymphopathia venereum,[5] sulfone administration,[6] and with streptococcal infections of the upper respiratory tract.[7] Perry[8] has recently presented an excellent review of the subject.

The incidence of erythema nodosum in this country is low in comparison to the reported incidence in the Scandinavian countries. During the five-year period of 1941 to 1946, I found the records of only six cases of erythema nodosum in the files of the Children's Hospital of Philadelphia* and of the St. Christopher's Hospital for Children. These cases, with one observed in private practice, supply the clinical material for the present report.

CASE 1.—E. W., a Negro boy, aged 7 years, was admitted to Children's Hospital of Philadelphia, May 29, 1942, with fever, swollen cervical nodes, and a swollen left testicle. He developed erythema nodosum two days after admission. Old tuberculin 0.001 mg. was strongly positive. A roentgenogram of the chest showed a density spreading out from the right hilum into the pulmonary parenchyma. The appearance was considered compatible with a diagnosis of pulmonary tuberculosis. Gastric washings were negative for tubercle bacilli. The erythema nodosum subsided in a period of ten to twelve days.

CASE 2.—M. W., a Negro girl, aged 8 years, was admitted to Children's Hospital of Philadelphia, May 28, 1943, with fever and tender swellings on the anterior surface of the lower legs of two weeks' duration. A diagnosis of erythema nodosum was made. Old tuberculin 0.001 mg. was strongly positive. Chest x-ray disclosed some enlargement of the cardiac silhouette. There was marked prominence of the left hilar shadow believed to be enlarged lymph nodes. Faint mottling was noted in the left infraclavicular region suggestive of tuberculous infiltration. The erythema nodosum subsided four days after admission.

From the Pediatric Department of Temple University, Philadephia.

*Records kindly furnished by courtesy of Joseph Stokes, Jr., M.D., Children's Hospital of Philadelphia.

These two patients illustrate the association of erythema nodosum with tuberculous infection. Wallgren[3] has shown that the great majority of children with erythema nodosum in Scandinavia have positive tuberculin reactions and that chest x-ray often shows evidence of tuberculous infiltration. Wallgren feels that the nodules develop at the time that tuberculoprotein sensitivity appears. He was able to demonstrate this fact with repeated tuberculin tests on a group of student nurses who had their first exposure to tuberculous infection while under his close observation. The erythema nodosum developed in these nurses coincidentally with the appearance of a positive tuberculin test.

As a result of Wallgren's work there has been a tendency to ascribe a tuberculous etiology to nearly all cases of erythema nodosum where patients have a positive tuberculin reaction. It seems likely that in some of these cases the positive tuberculin reaction is an incidental finding and that the erythema nodosum is due to a different etiologic agent. Löfgren[5] states that most workers in this field agree that unless the tuberculous lesion shows some evidence of activity, another cause for the erythema nodosum must be sought.

CASE 3.—L. S., a Negro boy, aged 8 years, was admitted to Children's Hospital of Philadelphia, Jan. 19, 1945, with a diagnosis of erythema nodosum. The throat and tonsils were noted to be moderately inflamed on admission. Old tuberculin 0.001 mg. was moderately positive.

This patient had been followed in the chest clinic since 1938 because of a positive tuberculin reaction. Serial roentgenograms of the chest had shown hilum densities considered to be compatible with tuberculosis.

The lesions cleared in eight days. Gastric washings were negative for tubercle bacilli. The chest x-rays showed no change during the illness with erythema nodosum.

It seems likely that the upper respiratory infection precipitated the erythema nodosum in this case and that the positive old tuberculin test was merely incidental. The fact that the chest x-ray remained unchanged is significant. Collis[7] has shown that some patients with erythema nodosum and negative tuberculin tests have marked skin sensitivity to streptococcal nucleoprotein. His findings have been confirmed by Coburn and Moore[9] who reported the production of exacerbations after the injection of the nucleoprotein of the hemolytic streptococcus intracutaneously. They found high antistreptolysin titers in twenty of twenty-two cases of erythema nodosum.

In spite of the fact that erythema nodosum has often been attributed to rheumatic infection, it is difficult to find cases in which rheumatic carditis was initiated by an attack of erythema nodosum. Wallgren[3b] described a patient who developed arthritis and carditis seven days after the onset of lesions. The carditis was confirmed by electrocardiographic changes. Mackenzie[2] reported twenty cases of erythema nodosum in patients with cardiac lesions. However, only five of his patients developed endocarditis during the attack. Rheumatic infection may be the etiologic agent in the following case report.

CASE 4.—M. F., a white girl, aged 8 years, was admitted to St. Christopher's Hospital, May 22, 1942, with a history of easy fatigability and pains in both thighs of two months' duration. There had been two spontaneous nosebleeds in the previous two months, and occasional abdominal pains. Reddish, painful lumps appeared over the anterior surfaces of both tibias three or four days be-

fore admission. Physical examination revealed no cardiac enlargement or murmur. There was no evidence of respiratory infection. The erythrocyte sedimentation rate was rapid. Old tuberculin 0.10 mg. was strongly positive. Chest x-ray revealed calcification within the hilum showing a healed first infection type of lesion. The lung parenchyma was clear. There was no cardiac enlargement. Electrocardiograms revealed a P-R interval of 0.16 second. The amplitude of the QRS complexes was low. Interpretation was myocardial depression.

It is difficult in this patient to decide whether the erythema nodosum initiated a mild carditis or whether it was just an incident in the course of a mild rheumatic infection. It seems unlikely that tuberculosis was a factor in this patient since the chest x-ray revealed a healed and calcified lesion at the hilum which remained unchanged during the erythema nodosum.

Sulfonamide admistration, especially the use of sulfathiazole, has been associated with the development of erythema nodosum.[6] Clinically and histologically the skin lesions show no differences from those associated with other disease processes. However, the distinguishing factor is the rapid disappearance of the nodules when the drug is stopped. The following cases were associated with the administration of a sulfonamide:

CASE 5.—R. W., a white boy, aged 6 years, was admitted to Children's Hospital of Philadelphia, April 23, 1944, with fever, malaise, and a purulent left otitis media. Sulfathiazole was administered 0.5 Gm. every four hours and after five days the temperature was normal and the child seemed improved. However, on the fifth hospital day an eruption typical of erythema nodosum appeared on the anterior surfaces of both tibias. Old tuberculin 0.01 mg. was negative. The sulfonamide medication was discontinued as soon as the nodules were noted, and in two days the lesions had cleared except for some discoloration of the skin.

CASE 6.—T. W., a white girl, aged 6 years, was admitted to Children's Hospital of Philadelphia, Nov. 14, 1943. History revealed that the patient had been ill three weeks before admission with an acute upper respiratory infection and otitis media which subsided with sulfadiazine medication. The complaint at the time of admission was fever and frequency of urination. Urinalysis revealed many pus cells with clumps in each high-power field.

The patient was given sulfathiazole 0.5 Gm. every four hours. The urine cleared promptly but on the third hospital day nodules typical of erythema nodosum appeared on the lower legs and a few on the forearms. Sulfathiazole medication was discontinued and the nodules completely cleared in five to six days.

Whether the erythema nodosum in these cases was actually due to the sulfathiazole administered or was due primarily to the infection for which the sulfonamide was given is a problem which lends itself to considerable speculation. Löfgren[10] thinks that the sulfonamide acts merely as an activator and that the infection is the primary factor in the development of erythema nodosum. The rapid disappearance of the nodules when the sulfonamide is discontinued argues in favor of sulfonamide sensitization being the primary factor.

The development of the nodules after the injection of Frei antigen in a case of lymphopathia venereum has been reported,[5] and similarly erythema nodosum has followed the application of a tuberculin test in a patient with

extreme tuberculin sensitivity.[5] It is unusual for it to result from diphtheria toxoid immunization, but the following case illustrates that it may be a possibility.

CASE 7.—W. M. a white boy aged 6 years, was seen in private practice Sept. 11, 1943, for a routine checkup and found to be in excellent condition. He had been immunized against diphtheria during infancy with alum-precipitated diphtheria toxoid injections. A booster injection of 0.5 c.c. alum-precipitated diphtheria toxoid was administered into the left upper arm at the end of the checkup examination.

Two days later the child was seen at home with a high fever, a red, tender, swollen, left upper arm, and nodules typical of erythema nodosum present over the anterior surfaces of both lower legs. The nodules followed the usual course, gradually fading during the next seven or eight days. Old tuberculin 0.01 mg. was negative and there was no evidence of an intercurrent infection of the upper respiratory tract.

In reviewing the literature, I found one other case of erythema nodosum which was apparently precipitated by the administration of diphtheria toxoid. Löfgren's[10] patient had a primary tuberculous infection of the right great toe with secondary enlarged nodes in the right groin. Following the administration of diphtheria toxoid, typical lesions of erythema nodosum appeared on the anterior surfaces of the lower legs. Löfgren felt that in his case the tuberculosis was the primary factor and the diphtheria toxoid merely the activator. In my patient, on the other hand, the injection of diphtheria toxoid in a previously immunized boy appears to be the primary factor in the development of the eythema nodosum.

COMMENT

The small group of cases presented illustrates the wide variety of etiologic factors associated with the clinical syndrome identified as erythema nodosum. The factor which is common to all the cases presented may be considered to be a nonspecific sensitization. This sensitization may be to tuberculoprotein, to the nucleoprotein of the hemolytic streptococcus, to coccidioidin, to the sulfonamide molecule, or to diphtheria toxoid. In addition should be mentioned the possible sensitization to the Frei antigen and perhaps to other antigenic substances.

It seems logical to conclude that erythema nodosum is not a specific disease but is more likely a reaction in a sensitized individual to a variety of sensitizing agents.

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BLOOD SUGAR IN NEWBORN INFANTS

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ALTHOUGH investigations of the blood sugar of newborn infants have been made, knowledge is still fragmentary concerning the accepted range of values during this period of life and concerning the influence of the method of determination on the values.

The purposes of the present investigation were: (1) to determine the change in mean blood sugar level of infants during the growth period from birth to the sixth day; (2) to determine the variability of the blood sugar level among normal infants and to ascertain whether this variability changes during the growth period; (3) to ascertain the variability which measured the error of the method, and (4) to compare blood sugar determinations as made by the micromethod and the macromethod.

REVIEW OF LITERATURE

The results reported in previous studies on blood sugar determinations in normal infants vary widely (Table I). This may be due to the variety of methods, the source of the blood samples, and the length of the fasting periods, as well as to the age of the infants. As indicated in Table I, the greatest reported range is from 0 to 0.32 Gm. per 100 c.c.; the minimal average value is 0.060 and the maximal average value is 0.126 Gm. per 100 c.c.

During the first week of life the blood sugar readings have been shown to be lower than at a later period. Miller and Ross[28] found low blood sugar values within the first forty-eight hours of life in infants who presented no abnormal findings. In McKittrick's[25] study of seventy-three normal infants, the mean blood sugar determination was 0.078 Gm. per 100 c.c. for the first week and 0.086 Gm. for the second week. These determinations were made on samples of blood taken three and one-half hours postprandially by the Folin method. Köhler[21] expressed a belief that variations in the blood sugar readings, as determined by Bang's method three to four hours after feeding, were closely associated with changes in weight of the infant. There was a decrease in the blood sugar readings until the third day; then a rise occurred. This fall was more rapid than the change in weight but the rise in blood sugar readings generally occurred two days before the weight increased. There appeared to be a leveling off of the rise between the seventh and the thirteenth days.

Götzky's[2] determinations of the blood sugar by Bang's method showed a rapid increase from the first day until the end of the first week, after which a gradual decrease took place until the twelfth day. Greenwald and Pennell[19]

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used the Folin micromethod to determine the blood sugar in samples of blood drawn three hours after the last feeding. The determinations were made on ninety-four infants whose ages varied between 1 and 10 days. These readings showed a slow but definite rise during this period.

Brown[13] found that the blood sugar values varied with age. On twelve infants less than 2 weeks of age, the blood sugar readings as determined by MacLean's method ranged from 0.072 to 0.097 Gm. per 100 c.c.; the average being 0.087 Gm. The infants older than 6 weeks had a blood sugar range of 0.086 to 0.116 Gm. per 100 c.c. and a mean of 0.106 Gm. Martinolli[17] found a significant rise in the blood sugar of 0.022 Gm. per 100 c.c. from the first to the seventh day of life, as did Bentivoglio.[16]

Others besides Köhler found a decrease in the values for blood sugar during the first three or four days of life. Ferri and Giudilli[23] showed that blood sugar determinations made on samples of blood drawn from twenty newborn infants four hours after feeding decreased until the third day. This decrease was 0.008 Gm. per 100 c.c. from the mean value on the first day to the mean on the third and fourth days. Schretter and Nevinny[18] found that the minimal blood sugar reading was made on the third day, after which the averages increased until the twelfth day. The determinations of capillary blood sugar on ten infants who were followed by Buonocore[31] showed a decrease from the mean of 0.0801 Gm. per 100 c.c. within the first eight hours after birth to the mean of 0.0727 Gm. on the second day, and then a gradual increase occurred to 0.0911 Gm. on the tenth day of life. However, Ketteringham and Austin[24] found a decrease from the average of 0.103 Gm. per 100 c.c. at birth to 0.067 Gm. in three to six hours; then a steady rise occurred in the average blood sugar readings to 0.076 Gm. on the third day. Sherman and his associates[14] found a slight decrease in the carbohydrate content of the blood between the first and the third day but after that time there was no apparent change. Hartman and Jaudon[32] found a very marked tendency for the blood sugar to fall into the hypoglycemic zone during the first day of life and these subnormal values persisted for several days.

Joslin and his associates[33] stated, without citing any evidence, that stabilization of the blood sugar level occurs during the first twenty-four hours of life. Reenkola,[26] using the Hagedorn-Jensen method, determined the blood sugar on samples of blood drawn from 100 newborn infants. The variability as determined by the standard deviation was 0.0170 Gm. per 100 c.c. one-half hour after birth, and then it decreased to 0.0109, 0.0146, and 0.0145 Gm. on the second, fifth, and eighth days, respectively. Since the variability decreased within the first two days of life, he interpreted this decrease as a sign of stabilization of the blood sugar level during this period. Schretter and Nevinny[18] showed that the difference between the maximal and minimal blood sugar readings decreased during the first week. This they interpreted as a sign of stabilization during the first week.

Buonocore[31] is the only one who made determinations of sugar on both the capillary and venous blood of infants. The values for the venous blood sugar were either equal to, or ranged to 23 mg. per 100 c.c. lower than, the values for capillary blood sugar.

TABLE I. FASTING BLOOD SUGAR VALUES IN NORMAL INFANTS

PUBLICATION		INFANTS			BLOOD SUGAR		
						GM. PER 100 C.C.	
AUTHOR	YEAR	AGE (DAYS)	NO.	HOURS OF FASTING	METHOD	RANGE	AVERAGE
Coblinei[1]	1911	9 to 21	7	3	Moeckel and Frank	0.076-0.098	0.085
Götzky[2]	1913	1 to 12	—	0.25 to 4	Bang	0.06-0.120	0.085
Mogwitz[3]	1914	7 hr. to 21	5	3.5 to 4	Bang	0.07-0.103	0.090
Heller[4]	1916	5 hr. to 9	12	0.25 to 4	Bang	0.060-0.133	—
Cannata[5]	1917	First 24 hr.	14	—	Lewis-Benedict	0.074-0.100	—
		2 to 5			Lewis-Benedict	0.076-0.094	
Sedgwick and Ziegler[6]	1920	3 to 43	45	Night	Folin	0.05-0.11	0.08
Spence[7]	1921	6 to 8 mo.	6	—	MacLean	0.080-0.112	0.096
Nyström[8]	1921	1 to 5	15	3.5	Bang	0.085-0.121	0.100
Lucas and associates[9]	1921	First 12	—	4	Folin-Wu	0.039-0.133	0.074
Mertz and Rominger[10]	1921	7 to 12	4	4	Bang	0.080-0.089	0.085
Rumpf[11]	1924	Infants	150	4 to 6	Bang	0.071-0.089	0.076
Muggio[12]	1924	—	16	3.5	Fontes-Thivelle	0.105-0.155	0.126
Brown[13]	1925	Less than 14	12	3 to 4	MacLean	0.072-0.097	0.087
Sherman and associates[14]	1925	1 to 5	16	—	Folin-Wu	0.090-0.125	0.102
Fedynski and associates[15]	1926	—	35	—	Hagedorn-Jensen	0.04-0.125	0.081
Bentivoglio[16]	1926	6 to 22	15	4	Bang	0.078-0.085	0.083
Martinolli[17]	1927	1 to 7	—	3.5	Bang		0.067 (1st day) 0.089 (7th day)

Schretter and Nevinny[18]	1930	1 to 12	38	2.5 to 3.75	Hagedorn-Jensen	0.033-0.146	
Greenwald and Pennell[19]	1930	1 to 10	94	3	Folin	0.060-0.100	0.076
Svensgaard[20]	1931	4 to 14	11	5 to 5.5	Hagedorn-Jensen	0.066-0.099	0.083
Köhler[21]	1932	1 to 13	40	3.5 to 4.5	Bang	0.034-0.092 (1st day)	0.060
						0.02 (later)	
Holman and Mathieu[22]	1933	1	51	—	Schaffer	0.050-0.170 (cord)	0.090
Ferri and Giudilli[23]	1935	First 5 or 7	20	4	Bang	0.055-0.173	0.085
Ketteringham and Austin[24]	1938	3 hr. to 3	37	—	Folin-Malmros	0.046-0.110	0.072
McKittrick[25]	1940	1 to 14	73	3.5	Folin	0.040-0.160 (1st week)	0.078
						0.055-0.118 (2nd week)	0.086
Reenkola[26]	1940	0.5 hr. to 8	100	3	Hagedorn-Jensen	0.036-0.120	0.073
Fumagalli[27]	1940	6 to 21	12	4	Hagedorn-Jensen	0.066-0.094	0.081
Miller and Ross[28]	1940	First 48	17	—	Folin-Malmros		0.0499
Zondek and Wolfsohn[29]	1941	First 6	23	3	Hagedorn-Jensen	0.0-0.32	0.060
							0.080
Hanley and Horn[30]	1943	1 to 6 hr.	129	—	Folin-Wu	0.052-0.095 (Macromethod)	0.066
						0.035-0.14 (Micromethod)	0.077
Buonocore[31]	1946	1 hr. to 10	10	4	Hagedorn-Jensen	0.47-0.120 (Capillary)	0.084
						0.047-0.116 (Venous)	0.076

PROCEDURE

Samples for determination of blood sugar were taken from each of fifty-one normal newborn babies daily for the first six days of life. Blood for the sugar determinations by a modification of Somogyi's micromethod[34] was obtained from a skin puncture in the heel of the infant. Two samples of blood were taken, each with a separate pipette, for each set of duplicate determinations. The first sample of blood was taken within the first twelve hours after birth. The subsequent samples were made at least four hours after the last feeding either in the morning before the 6 A.M. feeding or in the evening before the 6 P.M. feeding. One of the objectives of the study was to compare morning with evening readings, and another was to study the possible change of blood sugar with age in this period. It was, therefore, necessary not only that one-half of the readings for the six days of life of the infant be made in the morning and the other one-half in the evening, but also that the days of age on which these were made should be equally represented among the six days of life studied. The studies were, therefore, stratified in such a way that for some infants the observations alternated morning and evening; some of the observations were made in the order two morning, two evening, one morning, one evening; or some in the order two morning, one evening, two evening and so forth for all possible combinations.

The following procedure was used: To 4.1 c.c. of distilled water was added 0.1 c.c. of blood rinsed into this water. To this was added 0.4 c.c. of $Ba(OH)_2$ and the mixture was allowed to stand at least five minutes. Then 0.4 c.c. of $ZnSO_4$ were added. A finger cot was placed over the top of the tube containing the above mixture. The mixture was placed in the refrigerator and allowed to stand three to sixteen hours before the procedure was finished. In order to complete the determinations, the tubes were centrifuged three minutes. For the blank, 2. c.c. of distilled water and 2 c.c. of Somogyi's reagent were mixed. These tubes were heated ten minutes in a boiling water bath. When they were removed from the bath, 1 c.c. of Nelson's reagent[35] was added to each. The tubes were shaken immediately and allowed to cool to room temperature. The contents of each were made up to a volume of 25 c.c. with distilled water and mixed. The unknown was read against the blank in the spectrophotometer.

In order to compare the blood sugar determinations made by this micromethod with the determinations made by the macromethod of Folin and Wu,[36] 5 c.c. of venous blood were drawn from the internal jugular vein of some of the infants shortly after blood had been taken from the skin puncture in the infant's heel for determinations by the micromethod. No readings obtained by the Folin-Wu method were used if the blood contained any clots.

VARIABILITY

Variability of the Method.—Examination was made of the duplicate observations to estimate the size of the technical error. The data provided 306 sets of such paired readings (fifty-one infants times six days) which could be used for this purpose. The average value of the difference between the duplicates was 4.8 mg. per 100 c.c. Measured as standard deviation the technical error

was 4.4 mg. per 100 c.c.;* this represents 7.2 per cent of the mean value for the blood sugar; Fig. 1 shows graphically the variation represented by the technical error of the method.

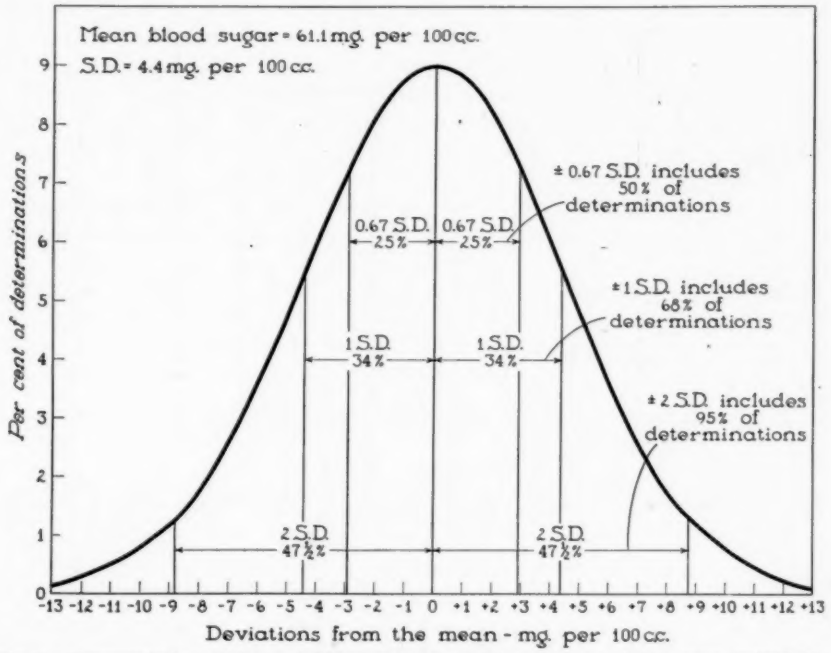
Mean blood sugar = 61.1 mg. per 100 cc.
S.D. = 4.4 mg. per 100 cc.
± 0.67 S.D. includes 50% of determinations
0.67 S.D. 25%
0.67 S.D. 25%
± 1 S.D. includes 68% of determinations
1 S.D. 34%
1 S.D. 34%
± 2 S.D. includes 95% of determinations
2 S.D. 47½%
2 S.D. 47½%
Per cent of determinations
0 1 2 3 4 5 6 7 8 9
-13 -12 -11 -10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 +1 +2 +3 +4 +5 +6 +7 +8 +9 +10 +11 +12 +13
Deviations from the mean - mg. per 100 cc.

Fig. 1.—Representation of the variability of repeated determinations on the same individual, based on 306 sets of duplicate determinations.

Macromethod and Micromethod Compared.—In order to confirm the differences between the blood sugar determinations made by the micromethod with the determinations made by the macromethod of Folin and Wu, fifty-four samples of venous blood were drawn from thirty-six infants shortly after blood had been taken from the skin puncture of the heel for determination of sugar by the micromethod. The mean value for the blood sugar determined by the Folin-Wu method was 66.8 ± 1.8 mg. per 100 c.c. and by the micromethod it was 59.4 ± 1.3 mg. The distribution of these fifty-four paired differences between the macromethod and the micromethod determinations is shown in Fig. 2. The mean differences were 7.4 ± 1.3 mg. per 100 c.c. and the standard deviation was 9.6 mg. The mean differences amount to about 12 per cent of the blood sugar values and are statistically significant. One should observe in Fig. 2 that although the differences indicate a large value for the Folin-Wu method, due to the intrinsic variability of the methods, the macromethod will appear to give a

*Each pair yields an estimate of the variance based on one degree of freedom, equal to one-half the squared difference of the two observations. The average of these is an estimate of the variance of the technical error, based on 306 degrees of freedom.

smaller value in about 20 per cent of the determinations when these two methods are compared. The fact that the variability for both methods, as measured by the standard deviation, was the same, affords confidence in the comparative precision of the micromethod.

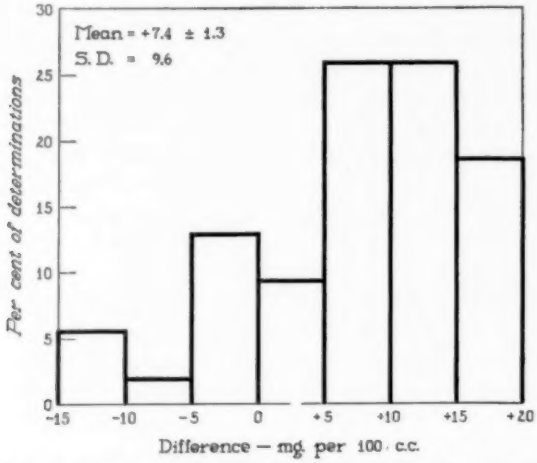

Fig. 2.—Distribution of differences between determinations by the macromethod of Folin-Wu and the micromethod.

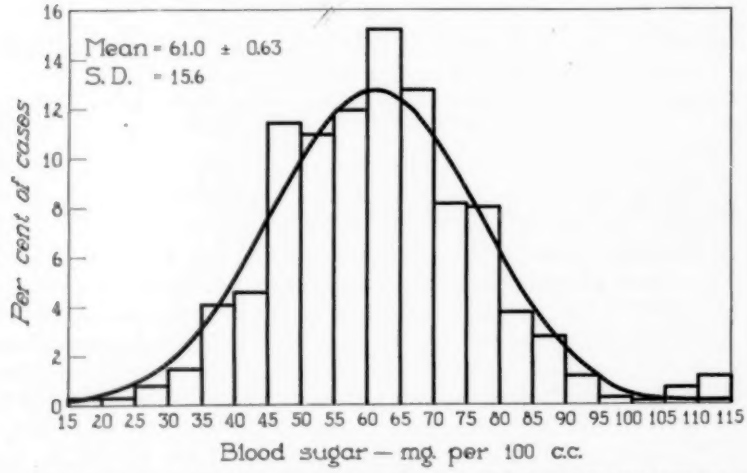

Fig. 3.—Distribution of 612 blood sugar determinations (micromethod) for fifty-one normal infants; comparison with the gaussian curve.

Variability Among Infants.—For the entire group of 612 determinations (fifty-one infants times six days times two duplicates) made for the fifty-one infants, the mean value was 61.0 ± 0.63 mg. per 100 c.c. and the standard devia-

tion was 15.6 mg. The corrected intraindividual variability* for these babies was 13.8 mg. per 100 c.c. (22.6 per cent of the mean) and the interindividual variability† was 7.0 mg. per 100 c.c. (11.5 per cent of the mean). The range of these readings was from 15.0 to 120.0 mg.; the low values were unaccompanied by any signs or symptoms of hypoglycemia. The distribution of these readings is compared with the gaussian or normal curve in Fig. 3. The observations appear to be satisfactorily represented by the normal curve.‡

Comparison of Morning and Afternoon Values.—A comparison of the blood sugar determinations was made between samples of blood drawn in the morning and those drawn in the evening (Table II). It was seen that the values for the sugar in the morning appear, on the average, to be somewhat higher than those in the evening (2.5 mg. per 100 c.c. or about 4 per cent of the mean). The difference is small and not quite statistically significant in the light of its error ($P = 0.06$) but it is possible that a larger sample would render it so. Such difference as exists is probably related to the length of the interval between the last feeding and the withdrawal of the blood, the morning readings having been taken, on the average, about four hours after the last feeding, the evening readings about five hours after the last feeding.

TABLE II. COMPARISON OF BLOOD SUGAR READINGS MORNING AND EVENING

OBSERVATION	NO.	BLOOD SUGAR (MG. PER 100 C.C.)	
		MEAN*	STANDARD DEVIATION
Morning reading	306	62.25 ± 0.91	16.0
Evening reading	306	59.76 ± 0.97	17.0
Difference	—	2.49 ± 1.34	—

*The number after the ± is the standard error of the mean.

Relation to Age.—When the blood sugar is examined in relation to the age of the baby (Table III, Fig. 4) it is seen that there is a distinct rise during the first six days of life. A line fitted to the data by least squares yielded the equation $S = 51.3 + 2.8A$ where S is the blood sugar in milligrams per 100 c.c. and A is the age in days. There is thus indicated an average daily increase of 2.8 mg. per 100 c.c. during the first six days of life. The observations showed a decrease from the first to the second day and from the fifth to the sixth day but these decreases are not statistically significant and probably represent random

TABLE III. COMPARISON OF THE DAILY BLOOD SUGAR READINGS

DAY OF LIFE	NUMBER*	BLOOD SUGAR (MG. PER 100 C.C.)	
		MEAN†	STANDARD DEVIATION
1	102	56.7 ± 1.6	16.4
2	102	54.8 ± 1.4	14.4
3	102	57.1 ± 1.2	12.0
4	102	62.1 ± 1.5	15.6
5	102	68.3 ± 1.7	17.0
6	102	67.1 ± 1.2	12.5

*There were two determinations at each observation and the number of individuals for each day was fifty-one.

†The number after the ± is the standard error of the mean.

*Variability of repeated determinations on the same infant.

†Variability between mean values for different infants.

‡Neither the "skewness" (0.02 ± 0.07) nor the kurtosis (0.21 ± 0.20), measuring departures from the gaussian curve, was statistically significant.

fluctuations rather than biologic changes. As has been noted previously, opinion has been expressed in the literature that the blood sugar values stabilize during the early days of life. As judged by the intradaily variability, measured as the standard deviation, there is no clear evidence that such stabilization occurs during this period. The average intradaily variabilitiy was 14.7 mg. per 100 c.c. or 24.1 per cent of the mean. During the first three days of life there was some indication of a lowering of the variability (16.4 to 12.0 mg. per 100 c.c.).

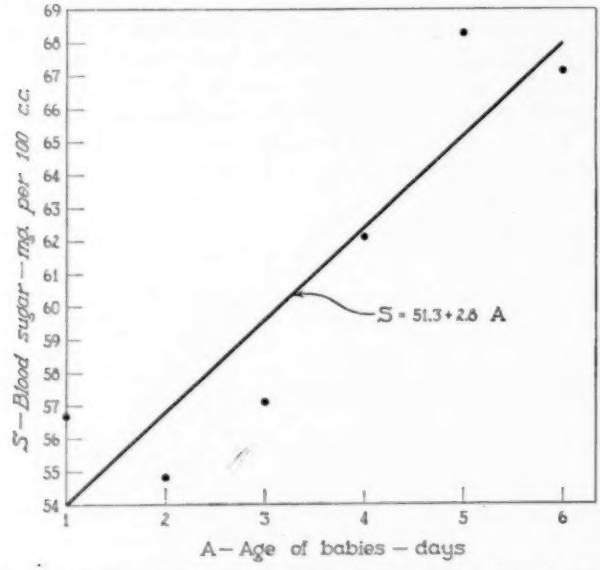

Fig. 4.—Mean value for blood sugar (micromethod) in relation to age. The regression line was determined by the least square method.

SUMMARY

Blood sugar readings on fifty-one normal newborn infants were made on duplicate samples of blood by means of a modification of Somogyi's method during the first six days of life. The technical error, measured as the standard deviation, estimated from the 306 differences between the duplicates, was 4.4 mg. per 100 c.c. (7.2 per cent of the mean). The average value for blood sugar as determined by the Folin-Wu method was significantly higher than the mean value for blood sugar as determined by the micromethod. For the entire group of 612 determinations the mean was 61.0 ± 0.63 mg. per 100 c.c. and the standard deviation was 15.6 mg. The corrected intraindividual variability for these babies was 13.8 mg. per 100 c.c. (22.6 per cent of the mean) and the interindividual variability was from 7.0 mg. per 100 c.c. (11.5 per cent of the mean). The range of the determinations was 15.0 to 120.0 mg. per 100 c.c. When the low values were obtained no signs of hypoglycemia were observed. The blood sugar determinations made on samples of blood drawn in the morning were higher than

those made on blood drawn in the evening, but not by an amount that is statistically significant, although perhaps a larger sample would have rendered it so. When the blood sugar was examined in relation to age, an average increase of 2.8 mg. per 100 c.c. per day during the first six days of life was found. There was no evidence of stabilization of the blood sugar during this period.

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POST-TRAUMATIC AMNESIC CONFABULATORY SYNDROME IN A CHILD

A Case Report and Discussion

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ALTHOUGH there is an abundant literature of post-traumatic psychotic reactions of the Korsakoff type in adults, few cases are on record of the occurrence of such a syndrome in children. Blau[1] stresses the point that none of the children described in his twenty-two case reports showed hallucinatory or confabulatory tendencies "which are so common in the acute traumatic psychoses of adults." Studies by Meyer,[2] Berger,[3] and Kasanin[4] did not include the occurrence of the syndrome in a child. A more recent report by Schilder[5] makes mention of the psychological significance of the post-traumatic behavior as expressed in hallucinations and dreams in which the patient sometimes "relives the traumatic experience." However, such occurrence was said to be limited to minor head injuries.

The following case report is noteworthy because it not only describes a rather typical amnesic confabulatory syndrome in a child but also illustrates a close relationship of the patient's post-traumatic behavior with pretraumatic emotional turmoil and conflict.

N. F., a 10-year-old schoolgirl, was brought to a Maryland hospital in an unconscious condition about one-half hour after she had been struck by an automobile after alighting from a bus. When admitted to the accident room she was in deep coma; however, there was no evidence of external injuries except for a small hematoma over the right frontal area and a tiny laceration in the left malar region. There was no bleeding from the ears and both tympanic membranes were intact. No escape of spinal fluid was evident from any orifice. The pupil of her left eye was somewhat larger than that of the right but both reacted promptly to light and the eye movements were unrestricted. No stiffness of the neck was present; however, abdominal reflexes as well as all tendon reflexes of both extremities could not be elicited. The Babinski was positive on the left side.

Blood pressure, temperature, pulse, and respirations were within normal limits and remained constant upon repeated examinations.

Though still profoundly comatose, the child became quite restless eight hours after admission. At that time her pupils were equal and there was no positive Babinski. All other reflexes were unchanged.

The child's comatose state continued for about twenty-eight hours, when she began to show responses to painful stimuli and at the end of forty-eight hours she executed certain direct commands, such as, "Stick out your tongue," "Open your eyes," etc.

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Laboratory findings one day after admission showed a red blood cell count of 4,500,000 with a color index of .85; the white blood cell count was 15,550 with seventy-nine per cent neutrophile, 17 per cent lymphocytes, 1 per cent monocytes, and 3 per cent myelocytes.

The examination of the urine showed no abnormality except for clumps of white blood cells.

Roentgen examinations of the skull and cervical spine were negative for fracture or dislocation. On the third hospital day, the patient responded to direct questions but seemed sleepy and stuporous. Abdominal reflexes were equal and active but tendon reflexes were still absent.

A spinal fluid examination showed normal pressure, 35 mg. per cent protein, normal sugar, and 27 lymphocytes.

On the fourth day drowsiness was still pronounced but the child began to repeat questions in an echolalic fashion. Examination of the eye grounds revealed 0.5 dioptric elevation of the left disc and a small area of detachment of the chorioretina in the same eye.

On the fifth day the patient suddenly sat up and seemed to be perfectly clear mentally. However, she knew nothing of her whereabouts or about the accident but recognized members of her family and recalled events of the past. The neurological signs began to improve and on the eighth day the edema around the left disc showed regression. Except for absent reflexes in the left lower extremity, there were no abnormal neurological findings.

On the eleventh day, for the first time since regaining consciousness, the child became restless. Her right pupil was now larger than the left and no reflexes could be elicited in the right lower extremity at this time. Her restlessness and hyperactivity continued for the next four days but her general condition seemed to improve when, in the late evening of the fifteenth hospital day she suddenly awakened from her sleep and fearfully told of seeing "snakes. bugs, and beetles of various colors" in her bed. She was completely disoriented and appeared extremely frightened. In spite of heavy sedation, she tried to climb out of bed and this behavior continued unabated, except for brief periods during which she was more lucid and could recall some events of the past and present; however, she showed a tendency toward filling memory gaps by making up a story in a confabulatory fashion. The child's confusional state grew increasingly more severe and careful neurological evaluations showed a constantly changing picture without definite evidence of a localized lesion.

Two additional lumbar punctures on the twenty-first and twenty-third hospital days, respectively, revealed clear fluid of normal pressure and a cell count of 2. A diagnosis of hematoma, subdural or epidural, was made and the patient transferred to the Johns Hopkins Hospital for surgical treatment.

Examination on admission showed the previously described hyperactivity, restlessness, and disorientation. There was a large hemotoma in the middle of the forehead but otherwise physical and neurological findings were normal. A spinal fluid examination was negative except for a cell count of 25. An electroencephalogram twenty-eight days after injury showed an irregular wave pattern with varied slow frequency of two-per-second waves to seven-per-second

waves. The occipital areas were out of phase with constant two- to three-per-second waves in the right occipital area and somewhat slower frequencies in the parietal and temporal regions. The slowing became more marked on hyperventilation (Fig. 1).

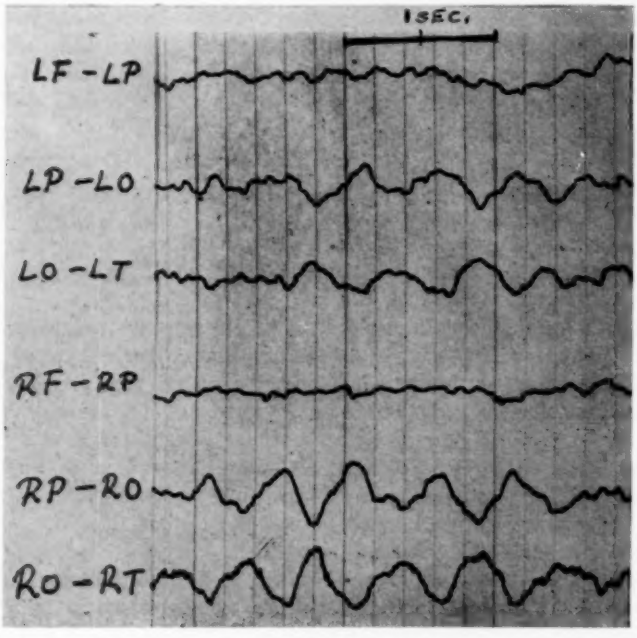

Fig. 1.—Electroencephalogram on twenty-eighth day. Bipolar tracing. (From the Electroencephalographic Laboratory, Henry Phipps Psychiatric Clinic. Dr. Leonard J. Gallant.)

On the basis of these findings, the neurosurgical consultant saw no immediate need for surgical intervention. Because of the persistence of the child's psychotic behavior and the increasing difficulties in management, a psychiatric consultation was requested. When the psychiatrist saw the girl, she was sitting in a chair staring at the floor. There was a marked flatness of facial expression and a striking absence of appropriate response to the people present. She answered questions rapidly but automatically and recalled past events without much difficulty. Without hesitation she told of being in a hotel at present, that it was in Baltimore and that she had dropped in because she just "happened to pass by." When asked where she ate her meals, the patient promptly replied, "I just go to places and eat. I guess this place is as good as any to stay in." Retention of digits was limited to four forward and there was a striking deficit in recall of immediate events. At times she showed perseveration of words with a tendency to become indignant when the examiner repeated an unanswered question. At such times the tendency to confabulate became more pronounced. The patient showed no recollection of the accident or the events that led up to it.

Information obtained from the child's father revealed that she had always been a very active, tomboyish child who enjoyed athletics a good deal but had few feminine interests. She liked to kick a football with her two older brothers, whereas she had little in common with her two-year older sister who is "the perfect young lady," according to the informant.

In her relations with other people she was somewhat shy but stubborn and independent. Her vivid imagination made her "dress up" many a story she told, which frequently annoyed her parents. She enjoyed listening to mystery stories on the radio and was an avid reader of "Dick Tracy."

Her birth and early development were normal. She progressed poorly in school during the first two years but subsequently improved her record.

Because of her interest in athletics, she had a tendency to associate with older boys and when she returned home one afternoon after having played with her friends she asked her mother what "fuck" meant. After the latter recovered from the initial shock, she inquired into the reason for her question and learned that the girl had been taking part in sex play with some of the boys, which caused her mother to be even more shocked. The mother then forbade the girl to leave the house until she had confessed to the priest; however, two days later, when the girl begged to be permitted to go swimming, her mother consented. It was during that swimming excursion that the accident occurred.

The father described himself as a rather worrisome and excitable person who is overly concerned about his children's health. His wife, on the other hand is calm and cool headed and an excellent manager of the home. There are no undue difficulties between the various family members, according to the father.

N's behavior in the hospital continued to fluctuate between periods of marked excitement with hallucinations of a visual and tactile nature, disorientation, and confabulation interrupted by relatively lucid periods during which she showed a marked memory deficit concerning recent events; however, the content of her hallucinations was of a rather constant pattern. She felt something "crawling in her pants," she saw blood in her pants, she looked for "these things" in her pants and dress, felt something "jabbing against her leg," adding that only a doctor could "jab something into her." The excitement became particularly marked during doctors' visits when she pulled her clothes off to "look for these things." She addressed one of them as "Dr. Virgin" and was quite flirtatious with him. She seemed particularly fearful of entering the bathroom and did so only after considerable persuasion. Another fear was to walk on grass and of bugs under the bed sheets. During episodes of severe excitement she yelled, "Don't beat me. I have to tell someone. I have to talk to someone."

This behavior pattern continued until the thirty-fifth day, when she calmed downed considerably and only occasionally showed hallucinations. However, there was still a marked memory deficit as regards recent events. She began to join in the group activities, was "show-offish" when talking with the doctors

and quite flirtatious with them. An electroencephalogram still showed abnormalities as described previously but was considerably improved (Fig. 2). She was discharged from the hospital on the forty-fifth day. Except for mild memory impairment, she had completely recovered.

The treatment while in The Johns Hopkins Hospital was primarily of psychiatric nature and consisted of about a dozen visits by the psychiatrist. As little emphasis was placed on formal testing as was consistent with an evaluation of her condition and the child was encouraged to express her fears in the treatment situation without obtaining verbal reassurance as such. The major source of emotional support for the patient was her private nurse who, under the guidance of the psychiatrist, provided the child with the personal attention so essential in her fearful state. Outside stimulation was reduced to a minimum, as were visits by her parents. As the patient grew calmer, she began to participate in games with other children with increasing self-confidence.

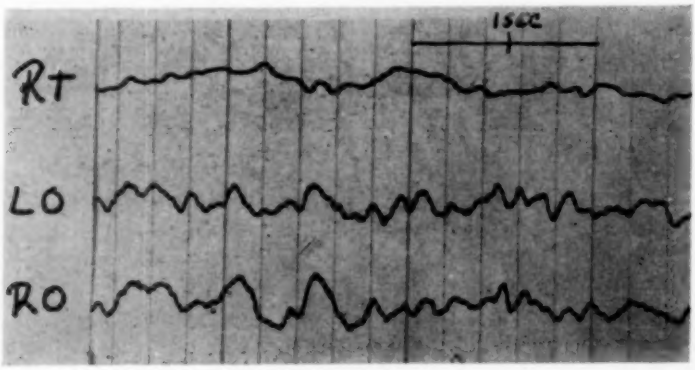

Fig. 2.—Electroencephalogram of thirty-fifth day. Monopolar tracing. (From the Electroencephalographic Laboratory, Henry Phipps Psychiatric Clinic. Dr. Leonard J. Gallant.)

In her relationship with the psychiatrist she displayed a playful somewhat uneasy assertiveness at first which was in contrast with her attitude toward various diagnostic procedures, during which she was quite serious and obediently cooperative. No attempt was made to encourage the child to verbalize emotional conflicts as it was not feasible, for geographical reasons, to continue treatment following discharge from the hospital. In addition, it was believed that her marked deficit state would not have been conducive to efforts of that type.

A follow-up visit one month after discharge revealed that the patient's memory had returned to normal even though she continued to be amnesic of the accident and events leading up to it. Her behavior had changed in so far as she had been less impulsive; however, she seemed considerably more "spoiled" and was thinking "that she could get away with everything at home as she could in the hospital," according to her parents. She remembered the three

principal physicians who took care of her and described the visiting pediatrician as the "one who liked the girls," the resident pediatrician as the "one who was handsome" and the psychiatrist as "that real smart one." During her visit she was somewhat uneasy and "show-offish," treated the doctor as a "pal," and at times playfully ignored his questions and suggestions. She complained of having been too much confined to the home and that her mother would no longer let her play with the boys "because of my sickness." She made no reference to the accident, however.

DISCUSSION AND SUMMARY

The preceding case report illustrates the occurrence of an amnesic-confabulatory syndome in a ten-year-old child on the fifteenth day following a severe head trauma after an initial five-day period of coma and semicoma and a ten-day interval of gradual but definite improvement. The manifestations of the patient's delirious reaction showed a direct relationship with certain pre-traumatic personal experiences and conflicts which were expressed symbolically in the patient's behavior and attitudes. With considerable personal support by physician and nurse in an accepting hospital environment, improvement was rapid and the child appeared to have completely recovered ten weeks after the accident.

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Erratum

In the article by Chute, Robinson, and Donohue, entitled "Cushing's Syndrome in Children," on page 20 of the January, 1949, issue of THE JOURNAL, the footnote should read "From the Departments of Pathology and Pediatrics at the University of Toronto and The Hospital for Sick Children, Toronto, Ontario."

Case Reports

ACCIDENTAL BENADRYL POISONING: REPORT OF A FATAL CASE

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THE so-called antihistamine drugs have had a wide and rather extensive use in the past few years. Various toxic and undesirable side effects such as drowsiness and dermatitis have been reported from their use, and in a few cases severe toxic symptoms and even death have occurred from marked overdosage.[1] Recently, a 2-year-old child accidentally consumed a quantity of beta-dimethylamino-ethyl benzhydryl ether hydrochloride (Benadryl), which caused his death.

CASE REPORT

A. L., a 2-year-old white male child, weight 27 pounds, was seen twenty or thirty minutes after his mother found him consuming the contents of a bottle of Benadryl (25 mg.) capsules. It was later determined that he took nineteen capsules; total dose, 474 mg. When first seen he was lethargic and respirations were shallow. Gastric lavage produced numerous large food particles; strands of partially liquefied pink gelatin could also be identified. The food particles continually plugged the tube and the lavage had to be terminated because of the poor condition of the patient, who was already cyanotic and showing convulsive movements. There was some emesis of gastric contents at this time. Caffeine sodium benzoate, 2½ grains, was given hypodermically, and the convulsive movements were controlled temporarily by the use of vinyl ether or ethyl chloride inhalations. As soon as enough anesthesia was given to stop the convulsions, the child became very cyanotic; oxygen, on the other hand, seemed to increase the seizures as it improved the cyanosis. Sodium phenobarbital, 2 grains, given over a one-half hour period, had no demonstrable effect. About two hours after onset the rectal temperature was 102.4° F. and pulse 110 to 120. He was transferred to the hospital where he was placed in an oxygen tent and given 5 per cent dextrose by clysis. Breathing was very shallow, and at times Cheyne-Stokes in character. He was completely unconscious, moderately cyanotic, and was having clonic convulsive movements of all extremities. The lips were dry, the pupils dilated and fixed. One hundred milligrams of sodium pentothal given intravenously caused some muscular relaxation and the pupils returned to normal size, but there was no real improvement in the child's condition. During the afternoon the temperature gradually rose to a high point of 107.4° F. in spite of cool sponges to the body, flushes, etc. The fever then dropped somewhat, but remained the rest of the time between 102° and 105° F. The extremities, however, were always quite cold to the touch. Respirations became very shallow and the pulse irregular. He was given alpha-lobelin and epinephrine as terminal measures, but the child expired approximately thirteen hours after he had taken the drug.

SUMMARY OF AUTOPSY REPORT

Autopsy was performed approximately seven hours after death and after arterial embalming. External examination revealed a well-developed and well-

From the Palo Alto Clinic, and the Department of Pathology of the Palo Alto Hospital.

nourished male infant measuring 38 inches in length and weighing an estimated 30 pounds. External examination was essentially negative except for slight postmortem hypostasis of posterior head and trunk, and presence of rigor mortis. Skin was generally clear but for the following exceptions: Recent venipuncture wounds in both antecubital fossae and diffuse swelling of both thighs with tiny puncture wounds anteriorly. There were no surgical scars. Superficial lymph nodes were not palpably enlarged. Trunk and abdomen were not remarkable. Feet were in a position of plantar flexion.

Internal Examination.—Subcutaneous fat was bright yellow and averaged 0.7 cm. over the abdomen. Abdominal organs showed the usual positions and relations. Liver edge was 3.5 cm. below the ensiform and 2 cm. below the right costal margin. Thymus was large with two symmetrical lobes, each measuring $8 \times 4 \times 1.5$ cm. Surface and cut section showed hundreds of tiny purplish-red petechiae. There was no evidence of tracheal deviation or compression. Trachea and larynx contained a small amount of brownish mucoid fluid resembling stomach contents, with similar material in main bronchi and major branches, without gross food particles. Lung borders were separated 5 cm. in the upper midline. Cardiac apex measured 4 cm. to the left of the midline at the fifth rib. There were a few drops of clear fluid in the pericardium. Heart was average in size, and showed about two dozen bright petechial hemorrhages over the epicardial surface of both ventricles posteriorly. The endocardium and valve leaflets were clear and the orifices were not dilated. The foramen ovale was closed. There was a single 2 mm. hemorrhage in one papillary muscle on the left side. The two lungs were essentially normal in size and configuration. There was mottled pinkish-purple discoloration over the posterior pleura on both sides, and cut surface showed confluent areas of red consolidation posteriorly. Frothy fluid could be expressed from the cut surface. Hilar lymph nodes were not enlarged, and pulmonary vessels were clear. Spleen and pancreas were not grossly remarkable. The colon contained soft brownish fecal material. Ileocecal region and appendix were not abnormal. Entire small intestine showed no gross abnormality. Duodenum contained flocculent mucoid fluid. The stomach was not distended or discolored, but was almost solidly filled with partly digested fruit and vegetable fragments mixed with brown fluid. Recognized among these were green berries with stems, bits of cabbage, celery, and apple. No remaining pills or fragments of capsule were found. Stomach mucosa was pale gray and softened, with some loss of mucosal markings. There were two bright red macular areas on the mucosa, without ulceration. Liver and gall bladder appeared grossly normal, except for moderate diffuse congestion of the hepatic parenchyma. Adrenals were average in size and symmetrical with thin yellow cortices. Both kidneys measured about $8 \times 5 \times 2.5$ cm. and showed a uniform pink cortex averaging 5 mm. and dark red pyramids. Pelves were not dilated but both ureters showed fusiform dilatation in the midportion, averaging 3 to 4 mm. in width against 2 mm. in remainder of the course. Bladder was filled with clear amber urine. Prostate was infantile.

Examination of the head revealed normal scalp and skull. The dura was pale gray and delicate, and lightly adherent to the skull cap. Inner meninges were delicate and translucent, with moderate congestion of the pial veins with dark blood. Hemispheres were symmetrically large with flattening of all convolutions and obliteration of the sulci. No definite cerebellar pressure cone found. On cut section, gray and white matter of the brain were well demarcated, but were soft and almost jellylike. There was slight injection of small vessels in the central white matter, but no focal softening or hemorrhage. Ventricular system was uniformly small and possibly compressed. Basal

ganglia, brain stem, pons, and cerebellum were not grossly abnormal. Pituitary was small and firm. Portion of spinal cord from the dorsolumbar region showed normal caliber and markings on cut section.

Microscopic Findings.—The heart showed the usual infantile structure. There were rare perivascular hemorrhages of microscopic size in the deep myocardium, and a larger perivascular hemorrhage in the epicardial fat of the left ventricle. Sections of lungs showed desquamation of bronchial mucosa with normal appearance of the submucosa and peribronchial glands. This suggested digestion by aspirated stomach contents. Lung parenchyma showed diffuse congestion of medium and small vessels, and extensive areas of alveolar edema and hemorrhage. There were a few large phagocytic cells in some alveoli, some of which contained fine carbon pigment. Medium and small bronchi contained a film of adherent leucocytes and granular brown amorphous material resembling bile pigment. There were small colonies of bacteria in the alveolar fluid in a few areas representing probable post-mortem growth. There was no evidence of pneumonia. The thymus showed multiple areas of fresh hemorrhage in the follicles and central pulp. Sections of thyroid, pancreas, and liver showed no significant change. The spleen showed evidence of necrosis in the Malpighian follicles, with amorphous eosinophilic material and granular basophilic fragmentation resembling nuclear debris replacing the central areas. There was acute congestion of the red pulp, but no areas of hemorrhage.

Sections of brain showed a somewhat spongy appearance of the cortical white matter with small clear vacuoles around many of the glial cells. There was a similar appearance in sections through the basal ganglia and wall of ventricle. Sections of pons showed marked increase in the perivascular space surrounding medium and small vessels, with a few areas of diapedesis of red cells. No areas of extensive hemorrhage found. The cerebellum showed no focal change. The Purkinje cells were well preserved.

The spinal cord showed marked perivascular edema surrounding the central vessels with necrosis of near-by nerve substance. This appeared more marked than any change in the brain itself and suggested terminal anoxia.

Summary of Autopsy.—Autopsy findings were similar to those in heat stroke with thymic and epicardial petechial hemorrhages, pulmonary congestion and edema, and passive congestion of liver and kidneys. There was evidence of gastric retention of partly digested food and terminal aspiration of gastric fluid in the trachea and bronchi. Findings in the brain were generalized cerebral edema and softening, with congestion of the pial veins. The microscopic findings confirmed the gross autopsy findings, with the addition of acute focal necroses in the splenic follicles, and perivascular necrosis in the spinal cord. Since autopsy was done approximately seven hours after death, and following embalming, the significance of the fine histologic changes were thought to be somewhat open to question. The presence of asphyxial hemorrhages above the diaphragm would suggest some interference with oxygenation, either as a direct effect of the drug, or possibly a result of terminal aspiration during the stage of coma.

DISCUSSION

Toxicity studies on animals[2] showed that death was produced in a few minutes to several hours after oral ingestion of Benadryl, and was preceded by violent excitement, convulsions, respiratory failure, and death. The development of hyperthermia is not specifically mentioned. With nonlethal toxic doses there was violent excitement but recovery was complete and prompt. When phenobarbital was given to rats before the administration of Benadryl, the

severe convulsions were prevented, but there was no improvement in the mortality rate. We felt justified in using the barbiturates in this case to control the convulsions even though it meant the use of a sedative drug in conjunction with an agent which itself also produces drowsiness and depression. The manufacturer, we learned later, specifically advises against the use of barbiturates even though convulsions are severe. These recommendations are based on at present unpublished experiments in monkeys where toxic doses of Benadryl and barbiturates were found to be a dangerous combination. The active measures of treatment that were recommended include evacuation of the stomach and gastrointestinal tract, hydration by all practical routes, and the encouragement of elimination through the skin by the application of warmth. Considerable effort has been expended in trying to find a specific antidote for the drug, but so far this work has been completely unsuccessful.

The fatal dose in our patient, 474 mg., or approximately 43 mg. per kilo., of which an unknown portion was eliminated by gastric lavage, is somewhat less than that found for experimental animals. The LD-50 for rats by the oral route was 545 mg. per kilo, and for intravenous administration, 45.7 mg. per kilo. In dogs, the LD-50 for intravenous administration is 30 mg. per kilo.

Finally, it seems worth while emphasizing the technical difficulty that sometimes attends the emptying of a child's stomach. The pieces of food, berries, etc., were so large that they could not be brought up by any stomach tube, and the child was so drowsy and depressed when first seen that it was impossible to make him vomit effectively.

SUMMARY

The accidental ingestion of 474 mg. of Benadryl by a 2-year-old child resulted in cyanosis, convulsions, cardiorespiratory depression, hyperthermia, and death. Autopsy findings were similar to those of heat stroke with petechial hemorrhages and cerebral edema. No specific antidote for Benadryl toxicity has been developed; symptomatic measures are discussed.

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POTASSIUM BROMATE POISONING: REPORT OF A CASE DUE TO INGESTION OF A "COLD WAVE" NEUTRALIZER

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POISONING due to potassium bromate, a toxic inorganic salt, is rarely encountered and only two case reports have come to our attention, one of which[1] was similiar to the case to be reported, and presented necropsy findings. This substance is used as the neutralizing solution in the "cold wave" home permanent process; according to the manufacturer it is a necessary part of the process and to date no adequate substitute has been found. It is to be expected that the number of cases of poisoning due to potassium bromate will be increased along with the widespread use of this permanent wave process in the home. In order that the medical profession be fully aware of its toxic potentialities the following case is reported.

CASE REPORT

M. L. N., a 2½-year-old white boy, was admitted to the Tucson Medical Center at 9 P.M. on June 18, 1948. He had drunk approximately one-half glass of the neutralizing solution of one of the cold wave processes eight hours previously. One hour after ingestion he vomited and was taken to another hospital where the stomach was lavaged with sodium bicarbonate. The child was discharged from that hospital but continued to vomit every one-half hour. At approximately 3 P.M. diarrhea ensued and up until the time of admission there were five loose, watery stools. The child had urinated several times and "the lips seemed blue." At 8 P.M. the temperature had risen to 101° F., and one of us (H. C. T.) was called, and the child was admitted to the hospital for treatment.

No previous history of kidney disease could be elicited.

On admission this well-nourished, well-developed child was extremely irritable but was otherwise not physically remarkable. There was no cyanosis. The blood pressure on admission was normal (96 systolic, 54 diastolic) and remained so throughout his entire course. The admission temperature was 100.2° F.

For the first twelve hours the child had no emesis and retained fluids by mouth. There was a yellow, semiformed stool with mucus and involuntary voiding of a small amount of urine. A dry, hacking cough developed.

The morning after admission the child vomited and was maintained for about eight hours on rectal fluids, following which infusions of 5 per cent glucose in Ringer's lactate were given.

It was noted on June 19 at 4:30 P.M. that the child had not voided since 4:30 A.M. Catheterization failed to obtain any urine. The child was increasingly restless and was vomiting every twenty to forty minutes. At 11:20 P.M. twitching movements of a few seconds' duration were noted in the right arm and leg, and by 11:45 P.M. the twitching motions were generalized and shortly thereafter became true convulsions lasting for about three minutes. These recurred every twenty to thirty minutes and by 1:30 A.M. were continuous despite heavy sedation and a lumbar puncture. Except for a few minor episodes, convulsions ceased until 3 A.M., when a generalized convulsion

of forty-five minutes' duration occurred. To combat anuria and prevent any dehydration by vomiting intravenous fluids were given. Failure to promote diuresis with these measures led to the use of 4 per cent sodium sulfate solution, reputed to be of value in these instances.

By 8 A.M. on June 20, edema of the face, hands, and feet was developing and the child was vomiting at fairly frequent intervals. By 6 P.M. the edema was generalized although ascites or pleural effusion did not develop. Anuria persisted from 4:30 A.M. on June 19 until 4 A.M. on June 20, when the child voided 90 c.c. of urine during one of his convulsive periods, following which he was again anuric. At 11:45 P.M. on June 21, 100.0 c.c. of hypertonic plasma were given intravenously and the dextrose and Ringer's lactate solutions continued as before. At 1:45 A.M. on June 21, two hours after the plasma had been given, the child voided 60 c.c. of urine and by 7 A.M. had voided 210 c.c.

Following the termination of the anuria the child progressively improved. Emesis became less frequent, the edema gradually diminished, and the urinary output increased until the child voided 750 to 1,000 c.c. on June 23.

The child was discharged on June 25 and when last seen on August 8 was well and happy. A previously noted anemia was still present. That there might still be some impaired renal function was evidenced by a total PSP excretion of 55 per cent in the one-hour volume of 250 c.c. of urine.

Laboratory Examinations.—

(See Tables I and II.)

TABLE I. URINALYSES

DATE	SP. GR.	ALBUMIN	W.B.C./HPF	R.B.C./HPF	CASTS/HPF
6-20	qns	3+	"loaded"	3-4	3-4
6-21	1.009	1+	10-15	occ.	12-15
6-23	1.004	trace	100-125	occ.	12-15
6-24	1.009	trace	60-75	0-1	few hyaline
6-25	1.005	trace	60-70	0-1	few hyaline
7-6	1.021	negative	4-6	0	0

TABLE II. BLOOD EXAMINATIONS

DATE	R.B.C. (MILLIONS)	HGB (GM.)	W.B.C.	NPN	PROTEIN (GM.)	PSP
6-19	3.90	11.4	15,500	86	—	—
6-20	—	—	—	118	—	—
6-21	—	—	—	114	—	—
8-6	3.48	10.7	3,600	34	7.7	55%

Treatment.—Therapy consisted mainly of sedation with 50 per cent magnesium sulfate, sodium phenobarbital, and chloral hydrate as indicated. Fluids consisted of an alternation of 5 per cent dextrose in normal saline, 5 per cent dextrose in distilled water, and 5 per cent dextrose in Ringer's lactate. The saline was discontinued when edema was noted. A solution of 4 per cent sodium sulfate was given intravenously to promote diuresis. Hypertonic plasma, prepared by dissolving lyophylized plasma with one-half the usual diluent, was given as another diuretic measure. Two hours after that had been given urinary excretion returned, but whether the sodium sulfate or the plasma was responsible cannot be determined.

DISCUSSION

Potassium bromate is almost an unknown to the medical profession and is infrequently mentioned in textbooks of pharmacology and toxicology. It is similiar to potassium chlorate but is estimated to be twenty to thirty times

as toxic for experimental animals.[2] Neither the chlorate nor the bromate ion is destroyed to any extent by the body, but both are absorbed from the gastrointestinal tract and excreted slowly by the kidneys almost in toto. These salts produce gastrointestinal irritation as evidenced by vomiting, cramping abdominal pains, and diarrhea. Absorption of the chlorate ion into the blood has produced destruction of erythrocytes and methemoglobinemia in experimental animals. This is probably not true for the bromate ion, though there is some evidence that it produces hemolysis in guinea pigs.

The slow, prolonged, renal excretion is probably a direct cause of the acute and subacute nephritis. In the case reported by Dunsky the necropsy findings revealed a predominence of tubular lesions while the glomeruli were almost uninvolved. The lesions were diffuse but he did not consider that they were an adequate explanation for the anuria in his case.

With the widespread use of home permanents—the number runs into the millions each year—and the fact that children are very liable to drink this colorless, almost tasteless solution, and that no antidote for potassium bromate apparently was known, the Toni Company, which manufactured the home wave sets, was contacted, as well as *Parents' Magazine*, whose Consumer Service Bureau had approved the process. The Toni Company sent a representative to investigate and it has been learned that research is in progress to determine antidotes for this poison. The research pharmacologist[3] suggested that the stomach acidity be neutralized to prevent the formation of the irritating hydrobromic acid and that a sodium salt be used to counteract "the toxic effects of potassium ion or substitute sodium bromate for potassium bromate." He also suggested the use of sodium thiosulfate to combat the oxidizing effect of the bromate ion.

The Toni Company representative[4] also states that the company is changing the format of the neutralizer package to emphasize more clearly the toxic nature of the product, and is also changing the directions for use so that the solution will not be allowed to stand around the house of the user for several hours.

SUMMARY

A case of potassium bromate poisoning due to the ingestion of a neutralizer solution used in one of the cold wave home permanents has been reported. The case was marked by protracted vomiting, diarrhea, convulsions of several hours duration, and anuria with azotemia. Treatment included the use of 4 per cent sodium sulfate and hypertonic plasma as diuretics. Recovery followed and the child is now living and well. The use of sodium thiosulfate as an antidote has been suggested.

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NEUROBLASTOMA (SYMPATHOGONIOMA) OF THE ADRENAL IN A NEWBORN INFANT

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A NEGRO female newborn infant died nine hours after delivery. Pregnancy and delivery were not unusual. Following delivery the baby had respiratory difficulty and was noted to be cyanotic. On admission to the Babies and Childrens Hospital shortly after birth, temperature, pulse, and respiratory rate were normal. The abdomen was greatly distended by a mass filling the epigastrium and both flanks, extending 3 cm. below the level of the iliac crests. Examination of the blood revealed 28,800 leucocytes per cubic millimeter and 30 per cent erythroblasts. The child died despite oxygen and stimulants.

Autopsy disclosed a neuroblastoma of the right adrenal with metastases to the liver, parapancreatic lymph nodes, and left adrenal. The liver extended 9 cm. below the costal margin in the right midclavicular line, displacing the intestines dorsally and inferiorly and elevating the diaphragms to the level of the fifth ribs bilaterally. The organ weighed 425.5 grams as compared with an average expected weight of 78 grams. The outer surface was nodulated by slightly projecting rounded masses, 3 to 8 mm. in diameter. In the cross section most of the liver was replaced by well-defined, generally circular, pale gray, slightly bulging, relatively soft, slightly moist nodules, variable in size and measuring from 3 to 5 mm. in diameter.

The right adrenal and tumor weighed 83.5 grams as compared with an average expected weight of 2.7 grams for the adrenal. It was attached to but did not invade the kidney. It displaced the right kidney dorsally and inferiorly and the duodenum ventrally and inferiorly. The tumor was lobulated, soft, and red. Penetration of the capsule was obvious. The left adrenal weighed 6.0 grams and contained several tumor nodules about 5 mm. in diameter.

Microscopically, the tumor is somewhat lobulated by fairly heavy bands of mature connective tissue richly supplied with capillaries. Most of the tumor cells are about the size of a lymphocyte, with dense nuclei and scanty cytoplasm. Some cells are slightly larger, with vesicular nuclei and a fair amount of cytoplasm. A few cells are multinucleated but there are no mitotic figures. Delicate fibrils are numerous and do not stain by the phosphotungstic acid method. There are many pseudorosettes with a centrally disposed mesh of fibrils surrounded by rims of tumor cells. There are numerous small hemorrhages and a few foci of necrosis. In the metastases the cell type is the same but lobulation is not distinct, connective tissue is not rich, vascularity is not great, fibrils are not numerous, and pseudorosettes are scanty. The small size of the cells of the tumor and the numerous fibrils in the adrenal tumor justifies classification as sympathogonioma rather than sympathoblastoma.

COMMENT

This case is unusual in that the tumor was obviously present during gestation. Neuroblastoma is a common tumor in the first decade of life, exceeded in frequency only by the leucemias and by embryonal carcinoma of the kidney, but it is rare at birth. An instance has been reported of its occurrence in a

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28-week fetus,[1] and one of fetal dystocia due to widespread hepatic metastases in a term infant.[2] It must be borne in mind in the diagnosis of hepatomegaly at birth since other diseases characterized by large liver, such as erythroblastosis fetalis and Gaucher's disease, rarely cause great enlargement of the liver until at least several hours after delivery or later.

There are two main types of metastasis: To the liver, which is said to occur in younger patients (average age 1½ years); and to the osseous system, particularly the orbit and calvarium, which is said to occur in older children (average age 3 years).[3] The two types are frequently present in the same patient and have neither clinical nor prognostic importance; thus the differentiation into "Pepper" and "Hutchinson" types of disease, and the attempt to predict the side of the original lesion on the basis of its metastases as has been done in the past is not justified.[4] The common presenting symptoms, then, are a mass in the abdomen, exophthalmos, or tumor of the skull. The primary tumor is rarely noted either by the patient or the parents. Frequently the diagnosis may be suggested by destructive lesions in the typical bony locations. The tumor is moderately radiosensitive[5] but almost invariably fatal within a year from the onset of symptoms.

SUMMARY

This is a report of clinical and post-mortem observations on a Negro female infant who died nine hours after birth with a large neuroblastoma of the right adrenal which had already metastasized to the liver, parapancreatic lymph nodes, and left adrenal. The microscopic features indicate that the tumor is a sympathogonioma, the most primitive form of neuroblastoma.

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GASTROESOPHAGEAL INTUSSUSCEPTION

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INTUSSUSCEPTION is the commonest cause of acute intestinal obstruction in children. It is primarily a disease of infancy, 80 per cent of cases occurring in the first two years of life and 50 per cent between 5 and 7 months of age. However, retrograde intussusception or invagination of the bowels from below upward is a rarity. There are only scattered case reports in the literature, and the diagnosis is usually made at operation or post mortem.

The following report is unique since not only was there a retrograde intussusception but in addition the stomach, which is rarely involved, was the site of the intussusception.

CASE REPORT

G. W., a 16-month-old Negro child, was admitted to Harlem Hospital on Dec. 8, 1946, with a history of waking during the night gagging and vomiting bright red blood. For supper the child had mashed potatoes and milk. As far as the mother knew no foreign bodies, medications, or corrosives were accessible to the child.

Past History.—The child had no previous serious illnesses. He had had a circumcision two weeks previous which was uneventful.

Physical Examination.—Physical examination revealed a well-developed and well-nourished male child who appeared somewhat sleepy and who was very comfortable except for intervals when he vomited copious amounts of mucus mixed with bright red blood. There were no bleeding points seen in the nose, mouth, or pharynx. The abdomen was soft, no masses were felt, and no tenderness was elicited, spleen and liver were not enlarged, and x-ray of the stomach and esophagus revealed no evidence of foreign body. Lungs were reported as negative.

Laboratory Data.—Red blood cells were 4.23 millions; hemoglobin 13.9 Gm.; white blood cells, 9,600 with 89 per cent polymorphonuclears, 3 per cent stabs, one per cent eosinophile; sickling preparation, negative; hematocrit, 52.2 per cent; specific gravity of blood 1.064. Temperature varied between 98 and 99.2° F. Pulse was 108 to 112, respirations, 24. To maintain water and electrolyte balances continuous clyses were given.

The child remained comfortable throughout the first and part of the second hospital day. Vomiting of bright red blood ceased after the first day and the only evidence of hemorrhage was a few small, dark brown spots seen about the bed sheet. Despite the infrequent vomiting on the second hospital day and the administration of continuous clysis, dehydration became quite pronounced. Toward the end of the second hospital day the child suddenly developed acute respiratory distress and expired within thirty minutes after this acute episode.

An autopsy was performed.

Gross Pathological Diagnosis.—Diagnosis was: (1) Intussusception of antrum of stomach into midesophagus with gangrene of intussusception and high intestinal obstruction; (2) acute passive congestion of lungs, liver, and

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splanchnic bed; (3) dehydration; (4) moderate fatty change of liver; (5) marked mesenteric lymphadenopathy. In the posterior mediastinum the esophagus at its midpoint is seen to balloon out suddenly to 2.75 cm. in diameter from the usual 1.25 cm. Palpation reveals it to be slightly boggy and firm. The dilatation continues to the stomach. The esophageal hiatus is free of defects and is bound in its usual tight manner to the wall of the esophagus. The stomach is invaginated by its central portion which apparently has traversed the stomach

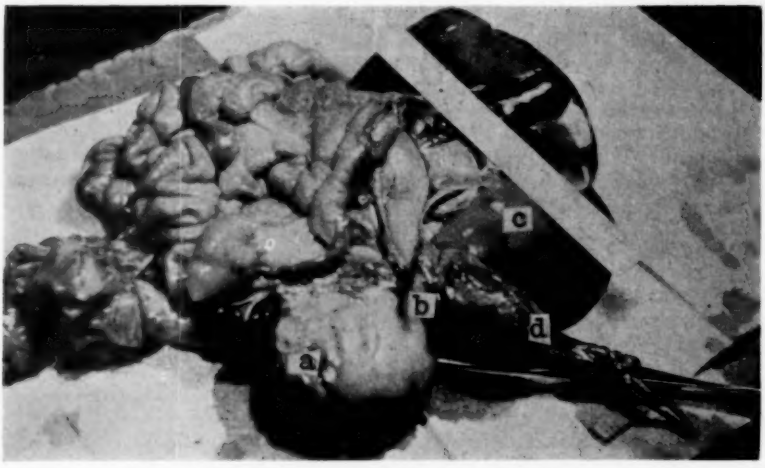

Fig. 1.—Anterior view. *a*, Greater curvature of stomach. *b*, Knuckle of stomach. *c*, Liver. *d*, Esophagus with intussusception.

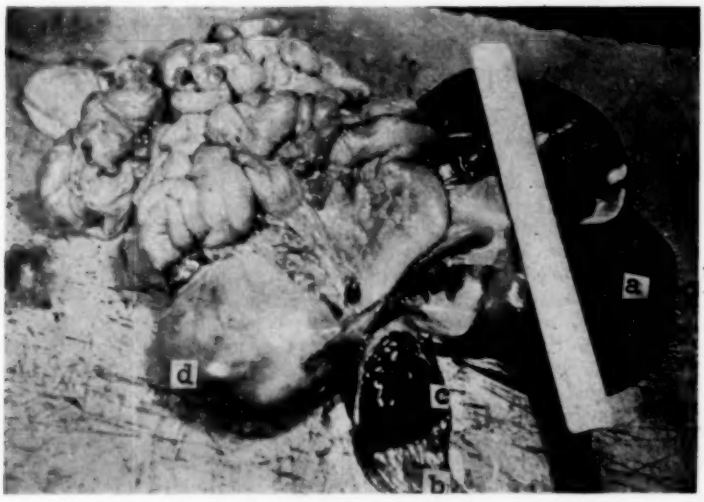

Fig. 2.—Anterior view after opening of esophagus. *a*, Liver. *b*, Esophagus. *c*, Intussusceptum. *d*, Greater curvature of stomach.

and now rests in the esophagus in an extensive intussusception. The first portion of the duodenum is slightly redundant, the remaining portions normal. The remaining bowel does not appear unusual.

The stomach presents the picture of marked intussusception of the antrum into and as far as the midesophagus. There is as a result a knuckle of stomach which extends about the intussusception from anterior to posterior aspects of the body of the stomach. The cardia, fundus, and greater curvature of the stomach are not involved in the intussusception. The lesser curvature and adjacent stomach and the lower half of the esophagus act as the intussusceptions. The pylorus is drawn up somewhat by the intussusception from its usual level at the first lumbar segment. There is no diaphragmatic herniation other than the intussusception. The duodenum is in its normal anatomical position except for slight upward movement of the first portion with the pylorus. The gastrocolic, gastrohepatic, and gastrosplenic ligaments are all without defect.

Fig. 3.—After dissection of esophagus, stomach, and pylorus. *a*, Esophagus. *b*, Antrum of stomach. *c*, Pylorus. *d*, Area intussuscepted (hemorrhagic). *e*, Esophagus with red area (where intussusceptum rested).

COMMENT

The normal difference in diameters between the small and large bowel and the course of peristaltic waves from above downward favor isoperistaltic intussusception. Occasionally, however, some local condition such as a tumor mass, Meckel's diverticulum, edema at the site of a gastrojejunostomy, a gastric diverticulum, chemical irritation, or even great abdominal distention may so alter conditions as to cause reverse peristalsis and make lumen of the small intestine relatively larger than that of the large bowel, thus producing a retrograde type of intussusception.

The case reported is unusual inasmuch as the stomach was the site of the intussusception and no visible pathogenetic factors were found to account for the development of a retrograde type of intussusception. The stomach is involved in an intussusception rarely, as a review of the literature indicates

1, 2, 4-9. The stomach is invaginated less often than the intestine because (a) it is well fixed at both curvatures, (b) its lumen decreases in the direction of the peristaltic movement, and (c) there are no wandering rings of contraction as in the intestines. The reported cases of intussusception of the stomach revealed predisposing etiologic factors in the majority of instances. Desternes and Baudon[1] found marked gaseous distention of the abdomen to have produced invagination of the stomach in their case. At operation a perforation of the stomach with adhesions to the liver was found. Cure followed surgical intervention. A polyp of the stomach was found by x-ray to be the cause of invagination in some of the reported cases,[5, 6, 8] and found on post mortem in another instance.[2] A diverticulum of the greater curvature was the point of origin of a gastroesophageal invagination as reported by Liaras and Ricard.[7] The stoma of a gastrojejunostomy was the site at which an inversion of the stomach occurred in another case report.[9] Experimentally it has been shown that the application of a mixture of .01 per cent silver nitrate plus 15 per cent sodium nitrate to the antrum of a dog's stomach caused edema of the area irritated and a retrograde gastrogastric intussusception resulted. Lannon and Culiner[4] reported the case of a 3- to 4-year-old child with a history of hematemesis and one that simulates our own case in almost every respect. On post mortem they found a retrograde intussusception of the lesser curvature, pylorus, and first part of the duodenum into the esophagus.

SUMMARY

This is a report of a case of retrograde intussusception in a 16-month-old male infant in whom the pyloric end of the stomach was invaginated into the esophagus. The outstanding symptom was hematemesis. Despite the decrease in vomiting and the usé of parenteral fluids, there was a continuous downhill course associated with an unrelieved high intestinal obstruction. At post mortem no etiologic factors were found which could have induced the development of this type of intussusception. The literature on cases of retrograde intussusception involving the stomach is reviewed and this case is an addition to the few cases reported.

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Psychologic Aspects of Pediatrics

CEREBRAL DAMAGE AND BEHAVIOR DISORDERS IN CHILDREN

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WITHIN recent years there has been a growing appreciation of the multiplicity of factors, both endogenous or individual and exogenous or environmental, which may cause disturbances of behavior in children. The current trend was forecast in 1938 by Lurie,[1] who decried the then prevalent attitude of attributing all disorders of behavior to "suppressions, frustrations, rejections, identifications, feelings of hostility, feelings of inferiority and inadequacy and the like." A breakdown by Lurie of the cases seen at the Child Guidance Home in Cincinnati showed that in 49 per cent of the behavior disorders studied there the underlying causative factors were endogenous or psychophysical in origin. In 28 per cent of the cases both endogenous and exogenous factors were operative, and in only 23 per cent were the causes primarily exogenous or environmental.

That cerebral damage of so mild a degree as not to give gross changes in motility or in the reflexes may, nevertheless, be the basis for disturbances of behavior in a certain number of children, is of special interest to the pediatrician. The causes of cerebral damage, encephalitis, head injuries, anoxia, etc., are conditions which we, not the psychiatrists, are called upon to treat; the symptoms of disturbed behavior are fairly characteristic; and the treatment is within the scope of the pediatrician.

The frequency with which cerebral damage and behavior disorders in children are related has not been estimated accurately but apparently it is not great. According to Bender[2] only from 2 to 5 per cent of the highly selected group of difficult problems sent to the Children's Observation Ward of the Psychiatric Division, Bellevue Hospital, are due to inflammatory encephalitis, and about 2 per cent more are related to head injuries. The incidence of postencephalitic behavior disturbances at the Child Guidance Home in Cincinnati is about 3 per cent. How often other types of cerebral damage are associated with behavior disturbances is not known.

ETIOLOGY

Behavior disorders have been observed with cerebral damage due to encephalitis, burns, head injuries, brain tumors, cerebral anoxia, and allergy. In addition, a large number of organic disorders of the brain may present themselves as behavior disturbances, e.g., myoclonic epilepsy, tic (Gilles de la Tourette), narcolepsy, tuberous sclerosis.

Encephalitis.—Changes in personality and behavior occur in a large percentage of all children following encephalitis. The symptoms generally become

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apparent immediately after the acute phase of the disease is over, although their appearance may occasionally be delayed for years. According to Ford,[3] in children under 3 years of age mental development is often completely arrested and imbecility or idiocy results. Children between 3 and 10 years of age show no striking reduction in mental capacity or evidence of gross neurologic disease but there may be marked aberrations in personality and behavior. The children are impulsive and destructive. They respond to the impulse of the moment without thought of the consequences. Undeterred by natural inhibitions or fear of punishment, they may lie, steal, destroy property, set fires, and commit sex offences. They make no effort to escape detection and, when asked about their misdeeds, they say that they could not help it. Although they show remorse which is often exaggerated, they continue to misbehave. They are, as a rule, indifferent to punishment.

The mood changes quickly. Sudden outbursts of temper may occur without any reason, during which the child may inflict physical harm on the persons about him. Depression, elation, and manic states are often seen. Some children show excessive and precocious sex interest.

A prominent feature of the postencephalitic child's behavior is hyperkinesis. The child is always on the go. Nocturnal insomnia and reversal of the normal sleep rhythm are commonly associated with the overactivity. Despite the apparent fearlessness, the children are often subject to night terrors and fears of imaginary persons. Older children may develop hypochondriasis.

Greenebaum and Lurie[4] describe the postencephalitic child as, characteristically, hyperactive, restless, and destructive, with a short attention span, highly distractible, lacking in self-control, and extremely unpredictable in his actions.

Burn Encephalopathies.—Generalized degenerative changes in the brain have been observed in association with extensive burns.[5] The clinical manifestations are those usually seen in children with diffuse cerebral damage, hyperkinesis, poorly patterned behavior, and inability to adapt to social demands. There is some interference with mental functioning which may be progressive. School adjustment is poor.

Behavior deviations associated with the cerebral damage should be distinguished from personality changes which result from the child's reaction to his prolonged hospitalization and to his disfiguring scars.

Head Injury.—Children withstand head injuries better than adults, among whom the presence of arteriosclerosis would seem to predispose to more serious damage.[6] In most instances psychic disturbances appear some time after the injury but occasionally there is an immediate reaction manifesting itself as an acute psychosis with excitement, marked impulsiveness, and restlessness over which the child has no control. Irritability and anxiety are prominent features. The children are amnesic from the accident but their memory is otherwise unimpaired and they are able to recognize parents, physicians, attendants, etc. normally. The psychosis lasts from two to five weeks and recovery is generally complete without sequelae.

The posttraumatic chronic disturbances may take the form of (1) a behavior disorder, (2) epilepsy with secondary deterioration, or (3) cerebral defect with secondary intellectual deterioration.

Behavior disturbances generally occur after severe trauma but they may follow apparently minor injuries. The syndrome resembles closely that of the postencephalitic. Though the personality changes appear shortly after the injury, the child may not come under observation until several years later. When the injury takes place during the preschool years the child's misbehavior is often tolerated at home and he is brought to the physician only after he starts to go to school and begins to get into trouble there.

The behavior disturbance is characterized by unusual changes in personality, the outstanding features of which are overactivity, restlessness, destructiveness, impulsiveness, assaultiveness, cruelty to animals, emotional instability, temper tantrums, truancy, and delinquency. There is no loss of mental power.

Posttraumatic epilepsy is a late complication and is sometimes susceptible to surgical treatment. Since convulsions occur only rarely after severe head injury, it is assumed that a constitutional predisposition is required. Ford[7] estimates that approximately 2 to 3 per cent of all cases of epilepsy are related to injury sustained at birth. Posttraumatic epilepsy in children frequently leads to secondary changes varying from mild personality disorders to marked mental and affective deterioration.

Posttraumatic mental defects are rare. They include the various forms of aphasia, defects of memory, and loss of intellectual power.

In evaluating the role of cerebral damage due to head injury, the possibility of a predisposing condition must always be kept in mind. Of eighty-six children who manifested behavior disorders associated with head injury, Fabian and Bender[8] found predisposing conditions in about one-fourth. Eight children were mentally retarded, five were epileptic, six suffered from some preceding type of brain damage, and two were psychotic. Fabian and Bender believe that "accident proneness" was an important factor leading to mishaps in their patients. The majority of their children came from a highly traumatic environment in which the parents were either alcoholic or were suffering from psychopathologic disorders.

Brain Tumors.—Disorders of behavior and personality associated with brain tumor are somewhat less frequent in children than in adults, owing, probably, to the rapidity with which tumors in children go on to produce definite signs of increased intracranial pressure and local damage.[9]

Keschner, Bender, and Strauss[10] described the disturbances in behavior of children with brain tumor. Of thirty-seven children under 14 years of age, approximately one-third showed personality changes. The most frequent manifestations were apathy, dullness, somnolence, poor cooperation, and inattention of a mild or transitory nature. In addition there were apprehension and depression, excessive crying, and temper tantrums. One child showed euphoria. In five, nonspecific personality changes were observed; that is, the parents described the children as "different persons."

Langford and Klingman[9] described three children with intracranial tumor, two of whom had posterior fossa tumors, one a craniopharyngioma. The most

frequent symptoms were anorexia, regressive behavior (a desire to be babied and waited on, jealousy not present before), listlessness, and withdrawal of interest from normal occupations. All three children were overanxious. They did well on psychometric examinations.

Cerebral Anoxia.—Cerebral anoxia, as a cause of cerebral damage during early life, is receiving increasing attention. In the adult, severe anoxia, whether from asphyxia by smoke, inhalation of carbon monoxide, gaseous anesthesia accidents, strangulation, or depressed respiration produced by drugs, leads to character change and memory defect. Schreiber[11] states that "with the knowledge that the specialized cells of the brain are identical in function in the infant, child, and adult, it is reasonable to assume that asphyxia produces analogous pathologic changes, possibly more destructive, in the younger tissue."

Windle[12] compared the behavior of guinea pigs in whom anoxia had been induced at or close to term by clamping the uterine vessels, with the behavior of littermates who had been delivered (through an abdominal incision) immediately before the induction of asphyxia. He observed that asphyxial conditions during birth produce severe changes in the central nervous system of the guinea pig. In general, the longer the duration of anoxia the more severe were the alterations, although the correlation was not as close as might be expected. In some animals asphyxia of even short duration led to changes, while in others prolonged asphyxia had only a slight effect.

Among the immediate effects encountered were decerebrate states, hyperkinesis, tremors, convulsive seizures, choreoathetoid movements, spasticities, paralyses, ataxias, somnolence, and impairment of sensory functions. As a rule the neurologic symptoms did not persist in marked form and were only transient. Many of the animals were inferior to their littermate controls in the maze tests. None was superior.

Schreiber[11] has found asphyxia to be the most common cause of cerebral damage associated with traumatic birth. Though the fetus and newborn, in the human as well as other animal forms, can survive degrees of anoxia that would be fatal in later life, the survival does not guarantee freedom from serious damage to nervous structure. Indeed, survival may be a mixed blessing.

In 1945 Preston[13] reviewed the histories of 132 children who had been anoxic at birth. One-fourth of these were mentally retarded. The remainder were of normal mentality but all showed deviate behavior. About 40 per cent of them were hyperactive, approximately the same percentage were apathetic, and about 20 per cent were epileptic.

Feeding difficulties were common during the early months of life and, as a consequence, the children were small and thin. Motor and speech development took place at the expected age, as well as bowel and bladder control. During the runabout age, sleep disturbances were common, the hyperkinetic children sleeping too little, the apathetic ones sleeping too much. Distractibility became evident at this age. Speech impurities and stuttering were common and memory was poor. Social contacts with other children were difficult to establish since the afflicted children were unable to conform to group play and suffered continual frustration. At school the early years were a tragedy, especially for the

bright children, since they were unable to concentrate and to cooperate in schoolroom routines.

On the whole there appeared to be a retardation in personality development, the school age child behaving like a runabout and the runabout like an infant. The hyperactive children developed an undesirable aggressiveness while the apathetic ones usually avoided conflicts with the world by excessively submissive behavior. At home the children demanded extra attention and as a result many of them were rejected. With the approach of adolescence, often earlier, there was a tendency toward improvement, in some instances complete.

In a recent report Stevenson[14] reviewed the records of 226 unselected children who are being followed in the Department of Maternal and Child Health of the Harvard School of Public Health by Dr. Harold Stuart and his group. He found a significant correlation between the physical condition of the newborn infant and his adjustment to his environment in later childhood, the children who had been in a poor state after birth showing a much higher proportion of poorly adjusted members than those whose condition had been good.

Pertussis.—The frequency of neurologic complications following pertussis was recently emphasized by Litvak and associates.[15] Forty-seven out of 6,002 children (0.8 per cent) admitted to the Kingston Avenue Hospital for Communicable Diseases showed gross neuropathy. One-half of the afflicted children were under one year of age, and this is the usual experience. The incidence of cerebral complications in this early group was about 2 per cent.

Lurie and Levy[16] observed definite behavioral, intellectual, and personality changes in thirty-four out of fifty-eight children who had had whooping cough during the first two years of life. The majority of the children first manifested their difficulties between the ages of 10 and 11 years, although in some the onset was even later. The etiologic relationship to pertussis was inferred from a thorough study and evaluation of all the physical, social, emotional, intellectual, constitutional, and hereditary factors that directly or indirectly might have had a bearing on the problems presented by the children. In many instances the developmental histories of the children indicated the sequential relationship between the attack of whooping cough and the retardation in their physical and mental growth. Twenty-five of the fifty-eight children in their group showed clinical signs of gross neurologic disease. Fifteen of the patients showed nerve deafness. Ten were definitely feebleminded.

A characteristic type of behavior disorder was not observed. A striking finding was a delay in the time of walking and talking. Seventeen of the thirty-four afflicted children showed extreme motor restlessness and impulsiveness with a tendency to destructive and unpredictable behavior.

Preston,[13] in her report on anoxic injury to the brain in early life, mentioned pertussis as the prime cause of anoxia in a number of her children with behavior disorders.

Rosenfeld and Bradley[17] have observed a characteristic clinical picture in a considerable number of children who had had pertussis during the first four years of life (i.e., before the fourth birthday). They attribute the behavior

disturbances to cerebral injury associated with the anoxia during the spasms. A similar clinical picture was observed in a group of children who had a history of difficult resuscitation at birth.

A variety of morphologic changes has been found in the brains of children dying of pertussis with cerebral complications. Hemorrhages are sometimes present. They are, however, usually not of sufficient extent to explain the symptoms. Inflammatory processes have been described but, according to Ford,[18] they are not consistent enough to justify a diagnosis of a true pertussis encephalitis. Widespread degeneration of the nerve cells in the cerebral cortex has been observed by a number of workers. In some patients with cerebral complications no morphologic changes in the brain are found. Hiller and Grinker[19] described a case in which the lesions were identical with those seen in carbon monoxide poisoning.

Cerebral damage in infants was the subject chosen by Dr. Harold Faber in 1947 for his presidential address before the American Pediatric Society.[20] The group which he studied were children in whom the presenting symptoms were mental deficiency, spastic paralyses, and convulsions. Cerebral atrophy was demonstrated by air encephalogram. In about one-third of his group the probable causative or contributory event took place before birth. In about 40 per cent the traumatic episode occurred in association with the birth process and in about 25 per cent the injury was postnatal. Faber considers the most important traumatic factor to be anoxia. It is his opinion that better obstetrics and better pediatrics could have prevented a considerable part of these disasters if present-day knowledge had been applied.

Allergy.—The view that disturbances of behavior may be etiologically related to the allergic process is favored by a large number of allergists and psychiatrists. The relationship was first suggested by Hoobler in 1916.[21] In 1922 Shannon[22] pointed out that allergic children were often restless, irritable, unruly, peevish, out-of-sorts, high-strung, and difficult to manage. He concluded that many of these symptoms result from irritation of the nervous system because of anaphylactic reactions to food proteins to which the patient is sensitized. Rowe[23] and others have stressed the changes in personality and behavior in allergic children. Randolph[24] emphasizes the relation of chronic food allergy to disturbances of behavior. In his experience the foods most commonly implicated are wheat and corn, although any food ingested repeatedly may be the offender.

Stevenson and Alvord[25] recently reviewed the subject of allergy in the nervous system. They concluded that allergic manifestations in the central nervous system may be produced by ingestion of food, inhalation of pollen, injection of serum, or vaccination against bacterial or virus diseases or as complications of various diseases. Experimentally a meningoencephalomyelitis, sometimes with disseminated foci of demyelinization, can be produced in ways strongly suggestive of allergy.

The clinical manifestations fall into two groups, (1) chronic fatigue, sluggishness, depression, and (2) instability, fretfulness, hyperkinesis, and hyperexcitability. The affected children are inclined to be unhappy at home and at school. School work is poor because of distractibility and impairment of mem-

ory. The children are generally looked upon as "nervous." Clinical evidence of allergy usually accompanies the psychic changes, but in some instances the disturbances in behavior may be the sole clinical manifestation. According to Randolph[24] removal of the offending foods from the diet results in improvement in behavior.

SYMPTOMATOLOGY

The symptoms of cerebral damage, whatever the etiology, are fairly uniform and characteristic. A prominent feature is hyperkinesis or hypermotility. The child is always on the move, touching objects, manipulating them, destroying them. The hyperkinesis leads the child, further, to seek continually to make contact with persons by clinging and overaffectionate behavior, by attention seeking, by nagging, and by abusiveness.

The mood varies unpredictably. Explosive outbursts of anger may occur without any apparent cause. Such reactions resemble the "sham rage" of Bard[26] which has been produced in animals by operations designed to release the hypothalamus from cortical control.

Children with cerebral damage are impulsive. The impulse of the moment is immediately translated into action without thought of the consequences. The children lie, steal, set fires, destroy property, and commit sex offences without apparent benefit to themselves and without regard to the consequences.

The attention span is short and the children are readily distractible. School work is likely to be poor for a number of reasons. Memory is variable, the child learning rapidly on some days, then seeming to forget everything he has learned on other days. There is inattentiveness and difficulty in adapting to the school room. Performance in arithmetic is especially poor.

Gesell and Amatruda[27] speak of a type of injury at birth which expresses itself in speech difficulties, notably stuttering, poorly defined unilateral dominance, and delayed integration. Later serious difficulty in learning to read may become evident. Oculomotor incoordination (e.g., strabismus) and visual defects are frequently associated symptoms.

Neurologic examination:[28] The usual signs of neurologic disease such as gross motor disability and changes in the tendon reflexes may be entirely absent. Postural and motility tests, however, often disclose significant alterations.

Evidence of organic brain disease may be elicited by observing the child in the standing position with the arms outstretched in front of him and the eyes closed. Attention should be paid to choreoathetotic movements of the hands and convergence or divergence of the hands, which indicate extrapyramidal involvement; spreading of the fingers, which is a sign of cerebellar disease; or a consistent lowering of one arm, which is indicative of muscle weakness (the dominant arm is generally held a little higher than the other). Having the child count while standing with the arms extended minimizes voluntary compensation for minor defects.

The child's motility is often characteristic of children of an earlier age. This can be observed best during the child's play. A method of bringing out primitive postural responses is carried out in the following manner:[29] The

child stands with the arms extended in front of him and his eyes closed. The examiner then rotates the child's head to one side. The primitive response to this test is to turn the body so that it is in line with the head. So long as the examiner continues to turn the head the child continues to turn on his longitudinal axis. This is normal for children from the time they are able to cooperate with the test until about 6 years of age. Thereafter the normal child will accept the turning of the head without rotating the body. After an initial displacement of the arms, he will correct the displacement.

The child with cerebral damage responds to this test like the younger child, rotating on his longitudinal axis as long as the head continues to be turned. A similar but exaggerated response, whirling, is obtained in the child with schizophrenia.

The brain-damaged child may show some dissociation of movements in walking and talking. In walking the customary swinging movements of the arms may be absent or irregular. Similarly, in the act of talking the normal smooth coordination between the act and respiration may be disturbed. The absence of appropriate facial expressions and associated gestures during speaking may also give an indication of organic brain disease.

Imperfect ocular convergence should be sought for. This is elicited by having the child try to converge on the finger placed on the end of his nose.

Occasionally abnormal muscle twitchings or tremors are observed.

Psychometric tests.[28] Children with organic brain disease have difficulty with tests which are dependent on spatial orientation, visual and auditory memory, and baragnostic sense (ability to distinguish weights). They are unable to copy a diamond (7-year-old test) and very young children are unable to copy a square. Memory for digits is poor, especially backwards. The children are unable to reproduce designs from memory and often fail to distinguish weights as well as one would expect from their general test performance. In reproducing designs from memory, a basic pattern suggestive of the original picture is generally made, but perseverative activity results in an almost endless repetition of the same primitive design.

Discrepancies between the performance on the Stanford-Binet test and on the Goodenough Draw-a-Man test are wide. A score of 2 years or more in the Goodenough test below that obtained in the Stanford-Binet is highly suggestive of organic brain disease. The ability to draw a man may, however, be unimpaired.

PSYCHOPATHOLOGY

It is not to be assumed that all of the symptoms observed in the brain-damaged child are organically determined. In good part the behavior is a result of the child's awareness of his inadequacies and his reaction to them. Bender[28] points out that, during the early months of life, the mother (or mother substitute) functions not only to give food, affection, and personal care to the child but she also gives him support in his motor activities. The infant is as much dependent on the mother for motor support as he is for food. In a brain-damaged child it may be necessary to supply this motor support for a much longer

period of time than normally, not only as far as locomotion is concerned but also in feeding, dressing, undressing, and even in speech.

Afflicted children tend to cling to the mother or a substitute and, as a result, they develop deep emotional attachments and dependency relationships. To a considerable extent excessive maternal care is actually a response to the child's real need. Depriving him of needed support may induce profound anxiety states. Thus the brain-damaged child may be retarded not only in his motor development but in his emotional development as well. The clinging and dependency made necessary by the motor defect have their counterparts in the emotional sphere.

The observations of Bender are based on a study of children with cerebellar dysfunction[30] which often exists in relatively pure form and is not complicated with other perceptual or impulse disorders. Similar conclusions to hers were reached by Schilder in his study of children with gross damage to the brain[31] and in his experience with adult obsessional problems.[32] He concluded that unsolved motor problems in early childhood may well be a factor leading to anxiety neurosis later on and may be connected with compulsive and obsessional neurosis.

One of the principal defects in the functioning of the brain-damaged child is an inability to integrate perceptions. Perception itself is not disturbed. The difficulty lies in synthesizing the perceptions into a logical whole. The child's dissatisfaction with his inability to make contact with his environment leads to increased attempts on his part to understand what goes on about him. This is expressed by hyperkinetic behavior, and the drive to touch, see, hear, feel, and finally to destroy every object which cannot otherwise be appreciated.

Anxiety is prominent in the brain-damaged child but it is generally concealed. It is of the diffuse, nonspecific type and often does not relate to real situations. Bender[28] explains the anxiety as the child's reaction to his own inadequacies. It is a factor intensifying his clinging behavior, his impulsiveness, and his overactivity.

DIAGNOSIS

A behavior disorder on the basis of cerebral damage must be differentiated from a disturbance due to exogenous causes, e.g., improper home environment, and schizophrenia. In favor of cerebral damage are:

1. History of an injurious episode usually in early life. (Gesell and Amatruda[27] have observed a group of infants who presented atypical behavior presumably on the basis of cerebral damage but in whom no evidence of abnormality in the birth or neonatal histories could be found.)
2. The symptom complex of hypermotility, impulsiveness, short attention span, rapid change of mood, variable memory, and poor performance in arithmetic.[17]
3. The absence of an emotionally traumatic home environment.
4. Changes in posturing and motility.
5. Changes in performance on psychometric tests.

The syndrome of schizophrenia in childhood is a complex one. It should be suspected when mental development which has been proceeding normally slows down or deteriorates. Mental development in the child with schizophrenia is likely to be irregular, the deviation affecting certain faculties, for example speech, more than others. Bradley[33] lists the symptoms of schizophrenia in children as follows: seclusiveness; irritability when seclusiveness is disturbed; day-dreaming and fantasies definitely in excess of what is usually seen in children of similar age and developmental status; bizarre behavior which consists of incongruous actions and activities such as repetitive, purposeless motions; unintelligible language and irrelevant expression of emotion; diminution of interests or failure to be attracted by objects and activities which one usually anticipates in children of similar age and intelligence; regressive personal interests or the voluntary selection of and participation in amusements and occupations which customarily intrigue children of younger age levels; sensitivity to comment and criticism (i.e., excessive emotional response to such personally directed opinions of others as praise, blame, etc.); and physical inactivity (i.e. conspicuously less gross motility than is commonly seen in other children of the same age and developmental status).

Electroencephalogram: Little in the way of diagnostic aid can be expected from the electroencephalogram. Although abnormal tracings are obtained in a high proportion of brain-damaged children, they are also often seen in children with simple behavior disorders.[34] There is nothing characteristic in the tracings of brain-damaged children. In a recent study by Levin,[35] children with post-encephalitic behavior disorders showed, for the most part, mild changes, principally of the slow wave type. A few showed severely abnormal tracings and occasional fast activity. Dees[36] observed electroencephalographic changes in a large number of children with asthma, which tended to become normal with control and improvement of the allergy.

Prognosis: The fact that a child's misbehavior is due to cerebral damage does not mean that the prognosis is necessarily hopeless or even bad. The outlook depends more on the extent of the cerebral injury and on the treatment than on the nature of the offending agent. The dominating drive in the brain-injured child, as in the well child, is toward normal maturation. This is a force capable of overcoming many obstacles.[28]

Preston[13] found the over-all prognosis in children with behavior disorders associated with anoxic damage to the brain to be good, especially if the diagnosis is made early and if proper treatment is instituted. In the group which she studied, once the parents and teachers came to understand that the child's misbehavior stemmed from a defect for which he was not responsible, much of the rejection was modified and greater tolerance was shown toward him. Gesell and Amatruda[27] have also observed a tendency toward improvement in children with minor cerebral injury.

Treatment: The child who misbehaves on the basis of cerebral damage needs, from the very start, an extra amount of maternal affection, attention, and support. The parents and teachers need to know that the misbehavior is

not the child's fault but that it stems from his defect. All along the line the child needs extra praise, encouragement and approval.

The advisability of nursery school attendance should be carefully weighed. The child should be allowed to attend only if he seems capable of giving a fair amount of attention and concentration. It may even be wise to postpone entrance into grade school.

Much can be done for these children prophylactically. Where there is reason to believe that a cerebral injury has been sustained, the child should be given extra support and affection before his symptom develops, even at the expense of setting up undesirably close emotional attachments and dependency relationships.

Benzedrine is a valuable therapeutic aid in some of these children. As an initial dose 5 mg. may be given daily once a day on rising to a 5-year-old child. The dose is increased rapidly until a therapeutic or toxic effect is obtained. Occasionally very large doses—up to 20 or 30 mg. a day—are tolerated.

SUMMARY

1. A disturbance in behavior may be the most prominent manifestation of cerebral damage of varying etiology in children.

2. The clinical syndrome is fairly characteristic.

3. Subtle neurologic changes and the performance on psychometric tests are diagnostic aids.

4. In general, the outlook for improvement in behavior and ultimate recovery is good.

5. Treatment consists of giving the child added support at home and in school in the form of extra affection, attention, approval, encouragement, and praise.

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The Social Aspects of Medicine

HOW "FREE HEALTH" WORKS OUT*

[**Editor's Note**: Last year the JOURNAL published several discussions of the British Medical Health Act which went into effect early in July, 1948. A number of reports have appeared recently discussing the working of the Act during its first six months. One of the most objective discussions appeared in the January 21 issue of the *U. S. News and World Report* and is reprinted with their kind permission.]

Boom in medical care in Britain shows what happens when the Government takes over all health services.

Some doctors are making more in Government service. Others find it costs them money. Specialists have most trouble.

But public likes it. Nearly everybody wants teeth fixed, tax-paid glasses, pills, a free checkup for the family.

IF BRITISH experience means anything, American doctors and the American public are due for surprises, when and if national health service is started in the United States.

The medical business, in light of British experience, then will enjoy an unprecedented boom. Dentists and opticians, in particular, will be swamped with customers. Income of many physicians, dentists, druggists, opticians, optometrists and others will grow, although work will be harder. Sick people often will find that they have to wait in line for hours to see a doctor, and that they must wait weeks or months to get into a hospital for a needed operation.

Socialized medicine is turning out to be popular in Britain. It is favored by most of the people and by many in the medical and dental professions. Lord Beaverbrook, who strongly opposed socialism for Britain, now says that "the national health scheme has been the greatest vote-winning success since Lloyd George introduced old-age pensions." But costs are high.

Britain is to spend the equivalent of $1,300,000,000 for the national health plan in its first 12 months. There are only one third as many people in Britain as in the United States. A similar plan for U. S., if no frills were added and payments for medical service were no higher than in Britain, would cost around $4,000,000,000 a year. With American standards, it could easily cost $5,000,000,000, and opponents claim it would run as high as $7,000,000,000. There is little prospect, however, that Congress will approve such a measure soon.

Doctors taking part in Britain's plan are paid the equivalent of about $3.25 per patient per year. They receive their pay from the Government once every three months. Dentists are paid by the Government according to the services they render.

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Some of the doctors, such as those in the poorer districts of London, enjoy an increased income under this system. If they serve the maximum of 4,000 public patients, they have an income of at least $13,000 a year, though they work harder and longer for that income.

But socialized medicine has hurt many other doctors whose patients were among the well-to-do. Under the rules, a doctor is supposed to be free to accept or reject patients, as he sees fit. But, in actual practice, he finds that he can't be as choosy about his patients as the regulations indicate. Besides, he is not free to charge what he wants, except where patients prefer to retain him on the old private basis.

A heart specialist, for example, whose income was above $20,000 a year in the past, now is trying to split his efforts between public and private patients. But he finds he is losing his private patients. If his private patients continue to drift away, he may not be able to carry on a mixed practice for long, and may be forced into full-time public work. In any case, his income is reduced. And those who still are willing to pay well for his services discover that he is unable to give them the time and attention he once did.

The lure of free medical care and free dental service has caused more than 90 per cent of the people in Britain to enroll under the national health plan. In unprecedented numbers, they are besieging the doctors' and dentists' offices for advice and treatment.

Dentists especially are in demand as never before. For many years, visitors to Britain have commented on the poor condition of British teeth and the small number of dentists available. When dentistry became free, a stampede ensued. The dentists began working 16-hour days. Their fees piled up and the income of some dentists has run as high as $40,000 or even $50,000 a year. Recently, the British Government has ruled that dentists must cut their fees in two after their gross income exceeds $19,000 annually.

Observers point out that the experience of British dentists might not be fully duplicated in the United States. The teeth of Americans have had somewhat better care than those of the British people, and the number of dentists per capita is greater in U.S. than in Britain. However, the British experience shows that, if free dental service were offered in U.S., a rush to the dentists' offices could be expected.

Many British doctors find life more exacting under socialized medicine. One, for example, reported that he was telephoned in the middle of the night by a man who had had a boil on his back for over a week and thought the doctor ought to know about it. Frequently, when a mother consults a doctor for herself, she takes along her smallest children and asks to have them examined, and also inquires about the care of older children in her family. This greatly increases the demands on physicians' time.

Free drugs and free health appliances are very popular, too. If a doctor approves, a patient is entitled to free eyeglasses, a free artificial leg, a free hearing aid, or even a free wig.

The optical business in Britian now is booming. Official estimates are that at least 90 per cent of the persons tested have been found to require glasses.

These are being provided at a rate of 7,500,000 pairs a year—nearly double the previous rate. But supply cannot keep up with demand, and a person entitled to glasses has to wait from one to three months before his order can be filled.

For many druggists, volume of business has doubled. Once a month, they report to the Government the number of free prescriptions supplied. The Government is trying to set an average price for a prescription to avoid a complex system in which each prescription, in each quantity, would be paid for separately. Pending the outcome of these negotiations, druggists are being advanced a flat sum equal to about 35 cents for each prescription filled.

People frequently find that they have to adjust themselves to the convenience of physicians and suppliers. After waiting in line in the doctor's office, the patient may find that the doctor shows little concern about his ailment. Or a person desperately ill at home may have trouble in persuading a doctor to call.

Delays are likely all along the line. Hearing aids have been supplied to only 5,000 of the estimated 150,000 persons in need of such assistance. Dental appointments often must be made weeks in advance.

Hospital facilities are short, too. Mothers are encouraged to have their babies at home, and hospital care is prescribed only in the event of necessity.

A small portion of hospital space is reserved for private, paying patients. For example, a person needing an operation for hernia can get that performed as a private service within a week. But, if he is a public patient and the operation is not urgent, he will have to wait, even up to several months.

One criticism is that a patient wishing the comfort of a private bed in a hospital and paying for it is not allowed to deduct from his bill the cost of a bed in the public ward.

Some people, who are getting better medical care than they previously could afford, welcome the benefits and do not complain about the delays. But the long waits are annoying to persons who were accustomed to prompt service in the past.

Apparently, many years will elapse before Britain has enough dentists, nurses, and hospitals to meet the demand for free health service. A similar situation could be expected in the U.S. if President Truman's health plan should be approved some day by Congress.

Over the long range, socialized medicine in Britian faces several hazards. The cost may prove greater than the public treasury can stand. The plan eventually may bog down under the weight of bureaucracy. If rewards are too meager, fewer young people may be attracted into the medical profession. Opponents of the plan predict that the end result will be a lower standard of medical care.

What the doctors in Britian, as in U.S., fear most is that, sooner or later, they will be forced into clinics to practice medicine, Russian style, at fixed salaries. It is too soon to predict the outcome of Britian's national health scheme. But the popularity of the scheme in its first six months seems to assure that it will get a long trial.

Comments on Current Literature

IRRADIATION OF LYMPHOID TISSUE IN DISEASES OF THE UPPER RESPIRATORY TRACT

DETAILED knowledge concerning the anatomy and physiology of the upper respiratory tract has emphasized the important part played by this region in maintaining the health and well-being of the individual: in the regulation of the temperature and humidity of the inspired air, the activity of the ciliated epithelium, the role of lymphoid tissue as a first line of defense against upper respiratory infection, in the production of antibodies and the process of immunity.

Proctor, Polvogt, and Crowe[1] have reported recently the results of an extensive study of lymphoid tissue in relation to diseases of the upper respiratory tract and the therapeutic irradiation of lymphoid tissue.

These authors point out that the real vulnerable point in the upper respiratory tract is the nasopharynx, since all air-borne organisms gaining access to the interior of the body pass through the nasopharynx and over the adenoids. The anatomical characteristics of tonsillar and adenoid tissue where crypts may be deep and intricate predispose to the retention of viable bacteria and the setting up of disease processes. Since there is no simple way to prevent air-borne organisms the nasopharynx may be the starting point for virus or pyogenic upper air passage infections and their complications.

In an effort to overcome these hazards to some extent, surgical removal of tonsillar and adenoid tissue has been practiced widely. However, while surgical removal has been beneficial in many instances, statistical studies indicate that such removal leaves much to be desired with respect to the subsequent incidence and severity of upper respiratory infection. Lymphoid tissue not only regenerates readily, but also is so much an integral part of the mucous membrane of the posterior and lateral walls of the pharynx and nasopharynx that all of it cannot be removed surgically.

In a discussion of the important protective mechanisms in the upper air passages, Proctor, Polvogt, and Crowe state that although lymphoid tissue is most abundant in the midline of the nasopharynx and in the fossa of Rosenmüller, "after surgical removal of adenoids in children nodules of this tissue often appear in and around the pharyngeal orifice of the eustachian tubes, in the choanae near the posterior end of the middle turbinates, and on the posterior and lateral surfaces of the vomer. These facts concerning the distribution of lymphoid tissue in the nasopharynx and posterior part of the nose are important for a clear understanding of recurring colds, of certain types of impaired hearing, attacks of suppurative otitis media and mastoiditis, ethmoiditis and chronic post-nasal discharge."

These authors advocate the use of irradiation by radon or radium applicator for the removal of recurrent lymphoid tissue following adenoidectomy and particularly for displaced nodules of lymphoid tissue in and around the pharyngeal orifice of the eustachian tubes that often lead to impaired hearing. They have employed this type of therapy in selected cases with increasing confidence and satisfaction for some twenty years. At first, irradiation therapy was used by them almost exclusively for the treatment of certain types of impaired hearing. However, as free beds became increasingly more difficult to obtain over the

years, they began to use this type of treatment for complaints which formerly were thought to justify operative removal of tonsils and adenoids. In selected cases they have found the procedure an invaluable therapeutic measure.

Details of the therapy are given and at the present time the Monel Metal Radium Applicator seems to be the instrument of choice. The authors state that well over 1,000 applicators are now in use in this country and that to their knowledge no complications arising from the procedure itself have been reported. Dosage is controlled carefully and undesirable secondary radiations are screened out.

During the studies carried out over the past five years, follow-up on many patients has been possible, especially among the group of children treated at the Hagerstown Clinic where more than 1,000 patients have been seen during this five-year period. A statistical study has been made on a group of 400. These children were treated with radium because of recurrent respiratory or ear infections, hearing impairment or bronchial asthma, and the authors feel that the treatment has been of major assistance in avoiding some of the most common serious problems of childhood such as ear infections and hearing impairment. In most of the 400 children included in this statistical study, the last examination was performed about one year following the completion of therapy.

More than 83 per cent of all children seen in this clinic because of hearing impairment had histories of recurrent otitis and upper respiratory infections thought to account for the impairment. The number of children whose hearing improved following irradiation amounts to nearly one-half of the group with impaired hearing before treatment. In a number it was possible to arrest progressive impairment and it is hoped that in some of these at least there will be improvement of hearing. Of the 400 children in this group, seventy-one underwent surgical removal of lymphoid tissue during the period of observation. In 191 patients lymphoid tissue had been removed surgically prior to their first clinic visit.

With respect to the treatment of children with bronchial asthma, Proctor, Polvogt, and Crowe state that the effects of irradiation have been difficult to evaluate. In a number of instances where the asthma was on an infectious basis, improvement in the asthmatic condition was dramatic. Careful consideration of all factors led them to conclude, however, that irradiation of the nasopharynx in bronchial asthma must be considered a helpful auxiliary to other forms of treatment, since infected adenoid tissue may be merely an accompaniment. Of forty-one children with bronchial asthma treated by irradiation of the nasopharynx, the average follow-up period has been thirty-five months. The majority of these children had desensitization therapy or other standard measures of treatment.

Clinical observation of the results of a treatment technique employed over a period of twenty-four years deserves attention and consideration. The results reported by the authors support amply their modest claim that while "irradiation of the naso-pharynx with a radium applicator is no panacea ---------- in selected cases it is an invaluable therapeutic measure."

RUSSELL J. BLATTNER.

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News and Notes

Dr. Abraham M. Litvak of Brooklyn, N. Y., died Jan. 30, 1949. He was chief of the pediatric service at Beth-El Hospital and associated pediatrician to the Jewish Hospital.

The **International and Fourth American Congress on Obstetrics and Gynecology** will be held in New York City at the Hotel Statler, May 14-19, 1949. Dr. Fred L. Adair of Chicago is Chairman.

A postgraduate course in pediatrics will be given by the Department of Pediatrics, University of Arkansas, Little Rock, on March 11 and 12, 1949. Guest speakers will be Dr. James G. Hughes of Memphis, and Dr. Myron E. Wegman of New Orleans.

The 45th annual conference of the State Department of Health and State Health Officers Association of New York will be held at Lake Placid June 20 to 23. The Association of School Physicians will hold its annual meeting on the opening day.

The officers of the **Rocky Mountain Pediatric Society** for 1949 are Dr. Wm. D. Rothwell, Jr., President; Dr. Mariana Gardner, Vice-President; and Dr. Edwin T. Williams, Secretary-Treasurer. All are from Denver.

A nine months' postgraduate course in pediatrics will be given at the Washington University School of Medicine beginning Sept. 12, 1949. Detailed information may be obtained from Dr. Merl J. Carson, Assistant Dean, Washington University School of Medicine, Euclid Avenue and Kingshighway, St. Louis 10, Mo.

The national report on the findings of the two- and one-half-year study of child health services is being published in two volumes by the Commonwealth Fund of New York. This publication will be marked by a dinner on April 2 in New York City. A nationally known layman and an outstanding authority in medicine and public health are being invited as guest speakers.

The **International Congress on Rheumatic Diseases** will be held in New York City from May 30 to June 3, 1949. In addition to papers by prominent American physicians, some 150 physicians from foreign countries are expected to attend, among them Lord Horder of London who will discuss rheumatism as a national problem.

Book Reviews

The Psychological Origin and Treatment of Enuresis. S. Smith, Ph.D., Seattle, Wash., 1947, U. of Washington Press, 70 pages. Price, $1.75.

Dr. Smith's monograph is intended as a guide for the parents of children with enuresis. There is little in the book which will be new to the physician. Unfortunately, most parents as well will derive little benefit from the book. The psychologic viewpoints presented are vague generalities which will serve only to confuse and frustrate parents who are hopefully seeking aid. Considerable space is devoted to a discussion, on the whole favorable, of "conditioning" methods of treatment such as the ringing of a bell or the release of a stream of cold water or air when the child wets. These methods have not found wide acceptance among physicians and their value is doubtful.

H. B.

Premature Infants. Ethel C. Dunham, M.D., Washington, D. C., 1948, Government Printing Office, 401 pages. Price $1.25. (Superintendent of Documents, Washington, 25.)

This is a very valuable book. The author, who has been interested for many years in the problems of prematurity, has carefully compiled and edited from a bibliography of over five hundred references a complete text of our present-day knowledge of the premature infant. The first section has to do with general considerations as the causes and prevention of prematurity, the growth and development, and the prognosis of the premature infant. Part two takes up clinical considerations as the physical care and environment, the feeding and nutritional problems, and finally the question of diseases. It is a reference book that should be on the shelf of every pediatrician's library as in it will be found the answers to most of the problems and questions that arise in regard to the premature infant. The Children's Bureau is to be congratulated in sponsoring the text and making it available to physicians.

Handbook of Pediatric Medical Emergencies. Adolph G. DeSanctis, M.D., New York, 1948, Privately Printed. Department of Pediatrics, New York Post-Graduate Medical School and Hospital. Price $2.00.

This is a very useful booklet of about ninety pages compiled by members of the pediatric staff of the New York Post-Graduate Hospital. The material has been accumulated over a period of years as a guide for residents and postgraduate students. The first section considers neurological emergencies such as coma and convulsions due to various causes, and their treatment. This is followed by emergency conditions of the cardiac, respiratory, gastrointestinal, and genitourinary systems. A most important section deals with various poisons and their treatment. A final section discusses miscellaneous emergencies as burns, hemorrhage, bites, etc. It does not pretend to be a text but fulfills its purpose of making information quickly and readily available as to how to handle pediatric medical emergencies. The treatment outlined under the various emergencies is sound and in keeping with recent medical progress. It is a booklet that could well be placed in the admitting room of every hospital. It may be obtained from the Secretary of the Pediatric Department, University Hospital, 303 East 20th Street, New York 3, N. Y.

EMIC. A Study of Administrative Experience. Nathan Sinai, Dr.P.H., and O. W. Anderson, Ph.D., Ann Arbor, 1948, School of Public Health, University of Michigan, 181 pages with 42 pages of appendix.

This is the report of a study of the administration of the EMIC program made by Dr. Sinai and his associates in 1943, financed by the New York and Marshall Field Foundations. The method of the Study was an analysis of the material and records in the Children's

Bureau and a field study in eight states from New York to California. Although the authors state "primary emphasis" was upon the field work, the report is chiefly based on the Washington end. It is purely a study of administration and does not concern itself with the more important problems of the quality of services rendered, except as an administration problem, nor the question as to whether a universally federal program is needed. The authors trace the constantly changing regulations and directions of an administrative nature issued by the Children's Bureau to meet the problems which developed as the program expanded and the difficulties which arose in adjusting the federal-state relationships. The problems of payment for service by physicians and hospital is discussed, including the unsuccessful attempt to establish geographic differentials. The authors are not so successful in their history of the program as so much has been omitted. That there was need for federal aid in a number of areas in the country as a result of situations created by the war is beyond question, as local services could not possibly meet the overwhelming demands for medical service thrust upon them. That there was need for a national program of federal payment for maternal and infant care is quite another matter. This report of EMIC considers it only as an administrative problem. If administrative experience in a national health program was the chief benefit from the program, the cost of over $130,000,000 seems rather high to say the least.

1948 Facts About Nursing. American Nurses Association, 1790 Broadway, New York, 106 pages. Price 35 cents.

This report of a survey of nursing contains a wealth of statistics regarding the nursing profession. There are today some 435,000 registered nurses but only about two-thirds are active. Tables of nurse distribution and student enrollment are among the many interesting subjects included.

Your Child or Mine. The Story of the Cerebral-Palsied Child. Mary L. H. Burton in collaboration with S. H. Jennings, New York, 1949, Coward-McCann, Inc., 64 pages. Price $1.25.

A small book containing the stories of six children with cerebral palsy of different types. It is not a medical text, but one intended to point out in a nontechnical way to the parents of children with cerebral palsy what can and cannot be done for them, and some of the psychologic and behavior problems which develop as a result of the handicap.

Baby Book. New York State Department of Health, 1948, 50 pages.

An excellent short book on infant care prepared by the Bureau of Maternal Child Care. About two-thirds of the text is concerned with parental attitudes in keeping with modern thought on infant care. Part II gives specific instructions as to details. An attractive, well-edited, and sound short book on infant care.

Editor's Column

THE PREVENTION OF DENTAL CARIES

PEDIATRICIANS have been questioned frequently the past few years about the topical application of fluorine to prevent dental caries. The reply has usually been that it is still in the experimental stage but that its value is seemingly being established by carefully controlled studies. Recently another method of topical application received widespread lay publicity which has made the entire matter quite confusing. After discussing the subject with several dentists, Dr. Virgil Loeb, a well-known stomatologist, kindly consented to put the gist of our discussion into letter form for publication in the JOURNAL. It is, we feel, a sane attitude which will aid the pediatrician in giving sound advice to parents.

January 17, 1949.

Dear Dr. Veeder:

Because the pediatrician is called upon so often to advise parents relative to the prevention of dental decay in children, and because the subject during the past few months has been given wide and, at times, confusing publicity in the press and in articles in magazines, I am very happy to tell you what I believe to be the present opinion of most dentists regarding the subject.

As you know, a great deal of scientific research has been undertaken on the cause of dental caries, and while much has been learned, investigators are still not in agreement. Undoubtedly there are both local and systemic factors which may be responsible, either singly or in conjunction with one another. Though the etiology is still undetermined, several methods to control and reduce dental decay have been suggested. The one which has been most broadly publicized during the past few months is the use of sodium fluoride. Research carried out by very able men in the U. S. Public Health Service and elsewhere on an organized basis has established the fact that this agent, when properly used, reduces the incidence of decay by from forty to fifty per cent. The exact mechanism through which fluorine produces a lowered caries rate is not known, but enough statistical evidence has been accumulated during the past five or six years to warrant the statement that it has great potential value in controlling dental caries and, when used properly by a dentist, it can do no harm. It must be noted that in connection with the fluorine treatment, regular visits to the dentist at from three- to four-month intervals are advisable, and that proper home care and proper diet are indispensable.

I believe it can be said that no single method of caries control has received such favorable response from the dental profession as has the fluorine therapy. Additional support has been given by editorial and other comments in the *Journal of the American Dental Association*, the official journal of the dental profession.

The general public was beginning to be aware of and take comfort from the sodium fluoride therapy when, on January 8, an article appeared in *Collier's*

magazine, describing the impregnation theory of Dr. Bernhard Gottlieb and ascribing ninety per cent favorable results to the use of his treatment. The claims of such a "miracle" medicine have naturally enough confused the public as well as many physicians and dentists, and it is very important that the results described be carefully checked. According to the *Collier's* article, the treatment "has been perfected and proved in the last few months," but there appears scant clinical evidence to support the claims. Physicians and dentists should await the results of much more investigative work before suggesting this impregnation method.

I believe that at the present time the dental profession prefers to advise and use the fluorine therapy rather than the more complicated therapy suggested by Dr. Gottlieb, principally because the former has been investigated for several years and the results of its use in thousands of patients are available. There is, as yet, inadequate clinical evidence to prove the claims of Dr. Gottlieb.

I trust this analysis may be of value to you.

Sincerely yours,
(signed) VIRGIL LOEB, M.D., D.D.S.

THE BRITISH MEDICAL HEALTH SERVICE

A LITTLE over six months have passed since July 5, 1948, when the British national health service went into effect. Reports vary somewhat but all are agreed it has cost much more than the original estimates. Glasses and dental services are way beyond expectations. Proponents of the plan argue that this shows the previous unmet needs of the British people, while opponents point to it as the grasping for something free. It was, of course, obvious from the start that the plan will have to be modified in the light of experience. A few weeks ago at a private dinner, a very high British official, who was the guest, was questioned as to the service and how it was working out. His reply was that it would take four or five years to really judge the value and success of the experiment, which was about as sound a judgment as we have heard. Most of the reports that have been coming back in recent weeks have seemed to us somewhat biased according to the attitude of the writer toward socialization as a political philosophy. The best report we have seen appeared in the January 21 issue of the *U. S. News and World Report*, which points out some of the problems that have developed, and which we have reprinted in the "Social Aspects of Medicine" column on page 383. Another brief account that we found of interest appeared in the January 15 issue of *The New Yorker* in the "Letter From London" by Mollie Panter-Downes. She makes one comment we have not seen elsewhere to the effect that some consider that "the Minister of Health, who is also responsible for housing, has put the cart before the horse. . . . The magnificient new machine of universal medical care can only, after all, do its best to patch up the effects of the appalling overcrowding and medieval discomfort in which thousands of displaced Londoners are still existing."